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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 9,012,462 B2

Attorney Docket No.: 209362-615035

Issued: April 21, 2015

Inventor: Yihan WANG et al.

For: PHOSPHOROUS DERIVATIVES AS
KINASE INHIBITORS

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PATENT EXTENSION
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The following Correspondence is submitted herewith:

1. Application for Extension of Patent Term Under 35. U.S.C. § 156 (in triplicate)
2. Exhibits A-J (in triplicate)
3. Fee Transmittal Letter (in duplicate)
4. Return Receipt Postcard

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On (date): June 21, 2017.

Respectfully submitted,

Date: June 21, 2017

Lin Yu

57,083

(Reg. No.)

For: Dale Rieger

43,045

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Commissioner for Patents
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Alexandria, VA 22313-1450

FEE TRANSMITTAL LETTER

FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156

Sir or Madame:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 9,012,462 B2, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

Exhibit A	Assignment Recordation and Assignment
Exhibit B	FDA Approval Letter
Exhibit C	Product Label
Exhibit D	Patent Term Adjustment from PAIR on June 16, 2017
Exhibit E	U.S. Patent No. 9,012,462 B2
Exhibit F	USPTO Communication: Redetermination of Patent Term Adjustment mailed February 22, 2017
Exhibit G	Request for Reconsideration of Decision of Redetermination of Patent Term Adjustment filed June 20, 2017
Exhibit H	Certificate of Correction issued June 6, 2017

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Signature

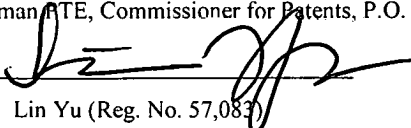
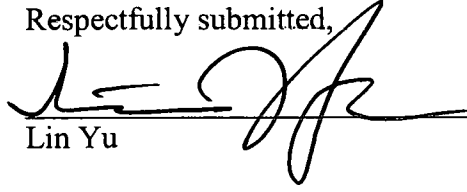

Lin Yu (Reg. No. 57,083)

Exhibit I Maintenance Fee Due Date Summary
Exhibit J Compendium of Significant Regulatory Activities in
Connection with ALUNBRIG™

Please charge the \$1,120.00 fee to Jones Day Deposit Account No. 50-3013.
The Director is hereby authorized to charge any additional fees, which may be required, or
credit any overpayment, to Jones Day Deposit Account No. 50-3013.

Date: June 21, 2017

Respectfully submitted,

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In re: U.S. Patent No. 9,012,462 B2 **Attorney Docket No.:** 209362-615035

Issued: April 21, 2015

Inventors: Yihan WANG *et al.*,

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FEE TRANSMITTAL LETTER

FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156

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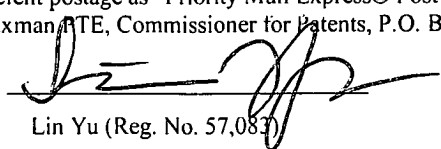
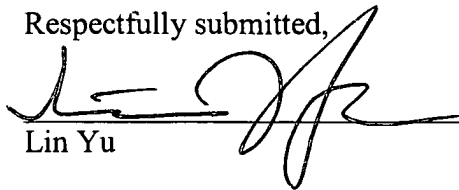

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Respectfully submitted,
Date: June 21, 2017

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For: Dale Rieger 43,045
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Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. § 156

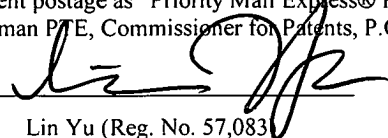
Sir or Madame:

Applicant, ARIAD Pharmaceuticals, Inc. ("ARIAD"), hereby requests an extension under 35 U.S.C. § 156 of the term of U.S. Patent No. 9,012,462 B2 ("the '462 Patent"). ARIAD is the owner of record of the '462 Patent by virtue of the assignment recorded at Reel 027097, Frame 0423. Exhibit A (Assignment Recordation and Assignment). ARIAD markets the product, ALUNBRIG™ (brigatinib), which is covered by the '462 Patent and was the subject of regulatory review. Exhibit B (FDA Approval Letter); Exhibit C (Product Label)

The following information is submitted in accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a).

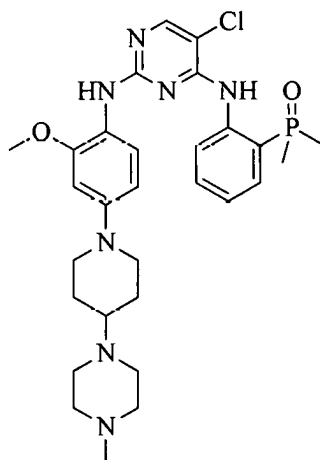
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Signature


Lin Yu (Reg. No. 57,083)

- (1) *“A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics”*

The approved product is ALUNBRIG™. Its generic name is brigatinib. And its chemical name is 5-chloro-*N*’-[2-(dimethylphosphoryl)phenyl]-*N*’-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, having the following chemical structure:



(hereinafter referred to as “brigatinib”). The molecular formula of brigatinib is C₂₉H₃₉ClN₇O₂P with a molecular weight of 584.09. Exhibit C (Product Label, “11. Description”).

The approved product, ALUNBRIG™, is a pharmaceutical composition comprising brigatinib as the active ingredient and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. Exhibit C (Product Label, “11. Description”).

- (2) *“A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred”*

ALUNBRIG™ was subject to regulatory review under section 505(b) of the Federal Food, Drug and Cosmetic Act (“FFDCA”).

- (3) *“An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred”*

ALUNBRIG™ received permission for commercial marketing or use by the Food and Drug Administration (“FDA”) pursuant to section 505(b) of the FFDCA on April 28, 2017. A

copy of the FDA approval letter is attached as Exhibit B and a copy of the Product Label is attached as Exhibit C.

- (4) *“In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum- Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved”*

The active ingredient in ALUNBRIG™ is brigatinib. Brigatinib has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

- (5) *“A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted”*

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being June 26, 2017.

- (6) *“A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration”*

The complete identification of the patent for which extension is sought is as follows:

Inventors: Yihan Wang, Wei-Sheng Huang, Shuangying Liu, William C. Shakespeare, R. Mathew Thomas, Jiwei Qi, Feng Li, Xiaotian Zhu , Anna Kohlman, David C. Dalgarno, Jan Antoinette C. Romero, and Dong Zou

Patent No.: 9,012,462 B2

Issue Date: April 21, 2015

Expiration Date: February 6, 2031¹

- (7) *“A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings”*

1. The expiration date is calculated based on the current PTA of 626 days as determined by the Office. Exhibit D (Patent Term Adjustment from PAIR on June 16, 2017).

A copy of U.S. Patent No. 9,012,462 B2 for which this extension is sought is attached hereto as Exhibit E.

(8) *“A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent”*

An Office Communication titled “Redetermination of Patent Term Adjustment” was mailed on February 22, 2017 in connection with the ’462 Patent. A copy of the Office Communication is attached hereto as Exhibit F. The Office Communication indicates that “[t]he Office has re-determined the PTA to be 626 days,” which is the same as the current PTA shown on PAIR. Exhibit D.

The relevant procedural history on the PTA determination is briefly described below. The ’462 Patent issued on April 21, 2015 with a PTA of 752 days. Patentee filed a request on June 22, 2015 for PTA redetermination. The Office mailed a decision on February 24, 2016, re-determining the PTA to be 436 days. Patentee filed a request on September 22, 2016 for PTA redetermination to adjust the PTA from 436 days to 591 days. The Office mailed a decision on February 22, 2017, re-determining the PTA to be 626 days. Exhibit F. On June 20, 2017, Patentee filed a request for reconsideration of the February 22, 2017 decision, requesting that the PTA be adjusted from 626 days to 591 days, a copy of which is attached hereto as Exhibit G.

A Certificate of Correction was issued on June 6, 2017, stating that “the term of this patent is extended or adjusted under 35 U.S.C. 154(B) by 436 days.” A copy of the Certificate of Correction is attached hereto as Exhibit H. The Certificate of Correction was apparently issued by the Office to reflect the February 24, 2016 PTA decision of 436 days, not the current PTA decision of 626 days.

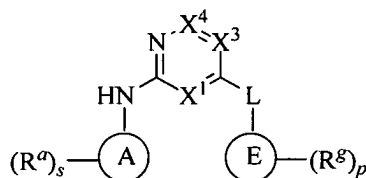
There are no disclaimers or reexamination certificates for the ’462 Patent. No maintenance fee in connection with the ’462 Patent is currently due. (Exhibit I).

- (9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:
- (i) The approved product, if the listed claims include any claim to the approved product;
 - (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and
 - (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product"

The '462 Patent claims, *inter alia*, the approved product ALUNBRIG™. More specifically, claims 1 to 3, 5 to 7, 9 to 12, 15, 16, 18 to 20, 24, 26, 28, 34, 36, 40 to 53, 56 to 58, 61 to 63, 66, and 72 of the '462 Patent read on the approved product, as described below:

Claim 1

1. A compound of the formula:



wherein

X^1 is NR^{b1} or CR^{b1} ;

X^3 is NR^{d1} or CR^{d1} ;

X^4 is NR^{e1} or CR^{e1} ;

Ring A and Ring E are each an independently selected aryl or heteroaryl ring, the heteroaryl ring being a 5- or 6-membered ring containing 1 to 4 heteroatoms selected from N, O and S(O)_r;

each R^a , R^b , R^d , R^e , and R^g is **independently halo**, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^{3a})_3$, $-NR^1SO_2R^2$, $-S(O)_lR^2$, $-SO_2NR^1R^2$ or $-NR^1SO_2NR^1R^2$; provided that at least one of R^a and R^g is or includes $-P(=O)(R^3)_2$ or a ring system containing $-P(=O)(R^3)-$ as a ring member;

and R^{b1} , R^{d1} and R^{e1} are **absent**;

or alternatively two adjacent substituents selected from R^d , R^{d1} , R^e , and R^{e1} , or two adjacent R^a form, with the atoms to which they are attached, a fused, 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4

heteroatoms selected from N, O and S(O)_r and which may bear up to four substituents;

L is O or **NH**;

r is 0, 1 or 2;

s is 1, **2**, 3, 4 or 5;

p is 1, 2, 3 or 4;

each **Y** is independently a **bond**, -O-, -S- or -NR¹-;

each **R¹** and **R²** is **independently** H or an **alkyl**, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, **heterocyclic** or heteroaryl;

each **R³** is independently an **alkyl**, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl, or two adjacent **R³** combine to form a ring system including a phosphorous atom;

each **R^{3a}** is independently an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic, or heteroaryl;

alternatively, each NR¹R² may be a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which can be optionally substituted and which contains 0-2 additional heteroatoms selected from N, O and S(O)_r; and

each of the foregoing alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and **heterocyclic** is **optionally substituted**,

or a pharmaceutically acceptable salt thereof.

Claim 1 claims the approved product. The required variables and values from claim 1 to read on the approved product are highlighted in bold in the claim above.

Claim 2

2. The compound of claim 1 in which:

(a) X¹ is N, X³ is N and X⁴ is CR^e;

(b) **X¹ is N, X³ is CR^d and X⁴ is CR^e**;

(c) X¹ is CR^b, X³ is N and X⁴ is CR^l; or

(d) X¹ is CR^b, X³ is CR^d and X⁴ is Cr.

Claim 2 depends from claim 1, which reads on the approved product. The required variables and values from claim 2 to read on the approved product are highlighted in bold in the claim above. Thus, claim 2 claims the approved product.

Claim 3

3. The compound of claim 1 in which **R^d** is selected from **Cl**, F, C1-C4 alkyl, trihaloalkyl, cycloalkyl, C2-C4 alkenyl, and alkynyl.

Claim 3 depends from claim 1, which reads on the approved product. The required variable and value from claim 3 to read on the approved product are highlighted in bold in the claim above. Thus, claim 3 claims the approved product.

Claim 5

5. The compound of claim 1 in which **s** is 1, **2**, 3 or 4, and each of the substituents **R^a** is independently selected from halo, **-R¹**, **-OR²**, **-NR¹R²** and **-P(=O)(R³)₂-** wherein each **R¹** and **R²** may be **further substituted** or unsubstituted.

Claim 5 depends from claim 1, which reads on the approved product. The required variables and values from claim 5 to read on the approved product are highlighted in bold in the claim above. Thus, claim 5 claims the approved product.

Claim 6

6. The compound of claim 5 in which at least one substituent **R^a** is **-OR²** and **R²** is selected from **C1-C6 alkyl**, C2-C6 alkenyl, and C2-C6 alkynyl.

Claim 6 depends from claim 5, which reads on the approved product. The required variables and values from claim 6 to read on the approved product are highlighted in bold in the claim above. Thus, claim 6 claims the approved product.

Claim 7

7. The compound of claim 5 in which at least one substituent **R^a** is a 5-, **6-** or 7-**membered heterocyclic** or 5- or 6-membered heteroaryl, **linked to Ring A** either **directly** or by an ether bond, and which may be **further substituted** with **1**, **2** or **3 substituents** independently selected from halo, **-CN**, **-NO₂**, **-R¹**, **-OR²**, **-O-NR¹R²**, **-NR¹R²**, **-NR¹-NR¹R²**, **-NR¹-OR²**, **-C(O)YR²**, **-OC(O)YR²**, **-NR¹C(O)YR²**, **-SC(O)YR²**, **-NR¹C(=S)YR²**, **-OC(=S)YR²**, **-C(=S)YR²**, **-YC(=NR¹)YR²**, **-YC(=N-OR¹)YR²**, **-YC(=N-NR¹R²)YR²**, **-YP(=O)(YR³)(YR³)**, **-Si(R^{3a})₃**, **-NR¹SO₂R²**, **-S(O)₂R²**, **-SO₂NR¹R²** or

$-\text{NR}^1\text{SO}_2\text{NR}^1\text{R}^2$; wherein each Y is independently a bond, $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^1-$.

Claim 7 depends from claim 5, which reads on the approved product. The required variables and values from claim 7 to read on the approved product are highlighted in bold in the claim above. Thus, claim 7 claims the approved product.

Claim 9

9. The compound of claim 2 in which:
(a) **X^1 is N, X^3 is CR^d and X^4 is CR^e** ; or
(d) X^1 is CR^b , X^3 is CR^d and X^4 is CR^e ;
and **R^d** is selected from **Cl**, F, C1-C4 alkyl, trihaloalkyl, cycloalkyl, C2-C4 alkenyl, and alkynyl.

Claim 9 depends from claim 2, which reads on the approved product. The required variables and values from claim 9 to read on the approved product are highlighted in bold in the claim above. Thus, claim 9 claims the approved product.

Claim 10

10. The compound of claim 2 in which s is 1, **2**, 3 or 4, and each of the substituents **R^a** is **independently** selected from halo, **$-\text{R}^1$** , **$-\text{OR}^2$** , **$-\text{NR}^1\text{R}^2$** and **$-\text{P}(=\text{O})(\text{R}^3)_2$** , wherein each **$\text{R}^1$** and **$\text{R}^2$** may be **further substituted** or unsubstituted.

Claim 10 depends from claim 2, which reads on the approved product. The required variables and values from claim 10 to read on the approved product are highlighted in bold in the claim above. Thus, claim claims the approved product.

Claim 11

11. The compound of claim 3 in which s is 1, **2**, 3 or 4, and each of the substituents **R^a** is **independently** selected from halo, **$-\text{R}^1$** , **$-\text{OR}^2$** , **$-\text{NR}^1\text{R}^2$** and **$-\text{P}(=\text{O})(\text{R}^3)_2$** , wherein each **$\text{R}^1$** and **$\text{R}^2$** may be **further substituted** or unsubstituted.

Claim 11 depends from claim 3, which reads on the approved product. The required variables and values from claim 11 to read on the approved product are highlighted in bold in the claim above. Thus, claim 11 claims the approved product.

Claim 12

12. The compound of claim 9 in which **s** is 1, **2**, 3 or 4, and each of the substituents **R^a** is **independently** selected from halo, **-R¹**, **-OR²**, **-NR¹R²** and **-P(=O)(R³)₂**, wherein each **R¹** and **R²** may be **further substituted** or unsubstituted.

Claim 12 depends from claim 9, which reads on the approved product. The required variables and values from claim 12 to read on the approved product are highlighted in bold in the claim above. Thus, claim 12 claims the approved product.

Claim 15

15. The compound of claim 11 in which at least one substituent **R^a** is **-OR²** and **R²** is selected from **C1-C6 alkyl**, C2-C6 alkenyl, and C2-C6 alkynyl.

Claim 15 depends from claim 11, which reads on the approved product. The required variables and values from claim 15 to read on the approved product are highlighted in bold in the claim above. Thus, claim 15 claims the approved product.

Claim 16

16. The compound of claim 12 in which at least one substituent **R^a** is **-OR²** and **R²** is selected from **C1-C6 alkyl**, C2-C6 alkenyl, and C2-C6 alkynyl.

Claim 16 depends from claim 12, which reads on the approved product. The required variables and values from claim 16 to read on the approved product are highlighted in bold in the claim above. Thus, claim 16 claims the approved product.

Claim 18

18. The compound of claim 10 in which at least one substituent **s** is a 5-, 6- or 7-**membered heterocyclic** or 5- or 6-membered heteroaryl, **linked to Ring A** either **directly** or by an ether bond, and which may be **further substituted** with **1**, 2 or 3 **substituents** independently selected from halo, **-CN**, **-NO₂**, **-R¹**, **-OR²**, **-O-NR¹R²**, **-NR¹R²**, **-NR¹-NR¹R²**, **-NR¹-OR²**, **-OC(O)YR²**, **-NR¹C(O)YR²**, **-SC(O)YR²**, **-NR¹C(=S)YR²**, **-C(=S)YR²**, **-YC(=NR¹)YR²**, **-YC(=N-OR¹)YR²**, **-YC(=N-NR¹R²)YR²**, **-YP(=O)(YR³)(YR³)**, **-Si(R^{3a})₃**,

$-\text{NR}^1\text{SO}_2\text{R}^2$, $-\text{S}(\text{O})_r\text{R}^2$, $-\text{SO}_2\text{NR}^1\text{R}^2$ and $-\text{NR}^1\text{SO}_2\text{NR}^1\text{R}^2$;
wherein each Y is independently a bond, $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^1-$.

Claim 18 depends from claim 10, which reads on the approved product. The required variables and values from claim 18 to read on the approved product are highlighted in bold in the claim above. Thus, claim 18 claims the approved product.

Claim 19

19. The compound of claim 11 in which at least one substituent **R^a** is a 5-, **6-** or 7-**membered heterocyclic** or 5- or 6-membered heteroaryl, **linked to Ring A** either **directly** or by an ether bond, and which may be **further substituted** with **1, 2 or 3 substituents** independently selected from halo, $-\text{CN}$, $-\text{NO}_2$, **$-\text{R}^1$** , $-\text{OR}^2$, $-\text{O}-\text{NR}^1\text{R}^2$, $-\text{NR}^1\text{R}^2$, $-\text{NR}^1-\text{NR}^1\text{R}^2$, $-\text{NR}^1-\text{OR}^2$, $-\text{C}(\text{O})\text{YR}^2$, $-\text{OC}(\text{O})\text{YR}^2$, $-\text{NR}^1\text{C}(\text{O})\text{YR}^2$, $-\text{SC}(\text{O})\text{YR}^2$, $-\text{NR}^1\text{C}(=\text{S})\text{YR}^2$, $-\text{OC}(=\text{S})\text{YR}^2$, $-\text{C}(=\text{S})\text{YR}^2$, $-\text{YC}(=\text{NR}^1)\text{YR}^2$, $-\text{YC}(=\text{N}-\text{OR}^1)\text{YR}^2$, $-\text{YC}(=\text{N}-\text{NR}^1\text{R}^2)\text{YR}^2$, $-\text{YP}(=\text{O})(\text{YR}^3)(\text{YR}^3)$, $-\text{Si}(\text{R}^{3a})_3$, $-\text{NR}^1\text{SO}_2\text{R}^2$, $-\text{S}(\text{O})_1\text{R}^2$, $-\text{SO}_2\text{NR}^1\text{R}^2$ and $-\text{NR}^1\text{SO}_2\text{NR}^1\text{R}^2$; wherein each Y is independently a bond, $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^1-$.

Claim 19 depends from claim 11, which reads on the approved product. The required variables and values from claim 19 to read on the approved product are highlighted in bold in the claim above. Thus, claim 19 claims the approved product.

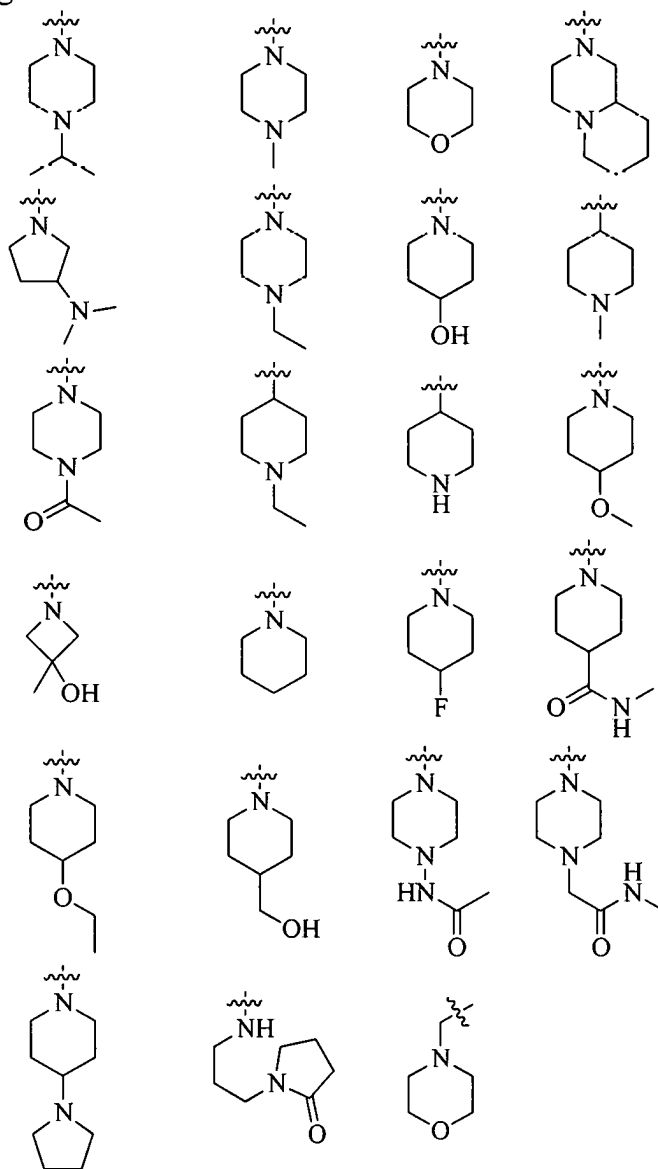
Claim 20

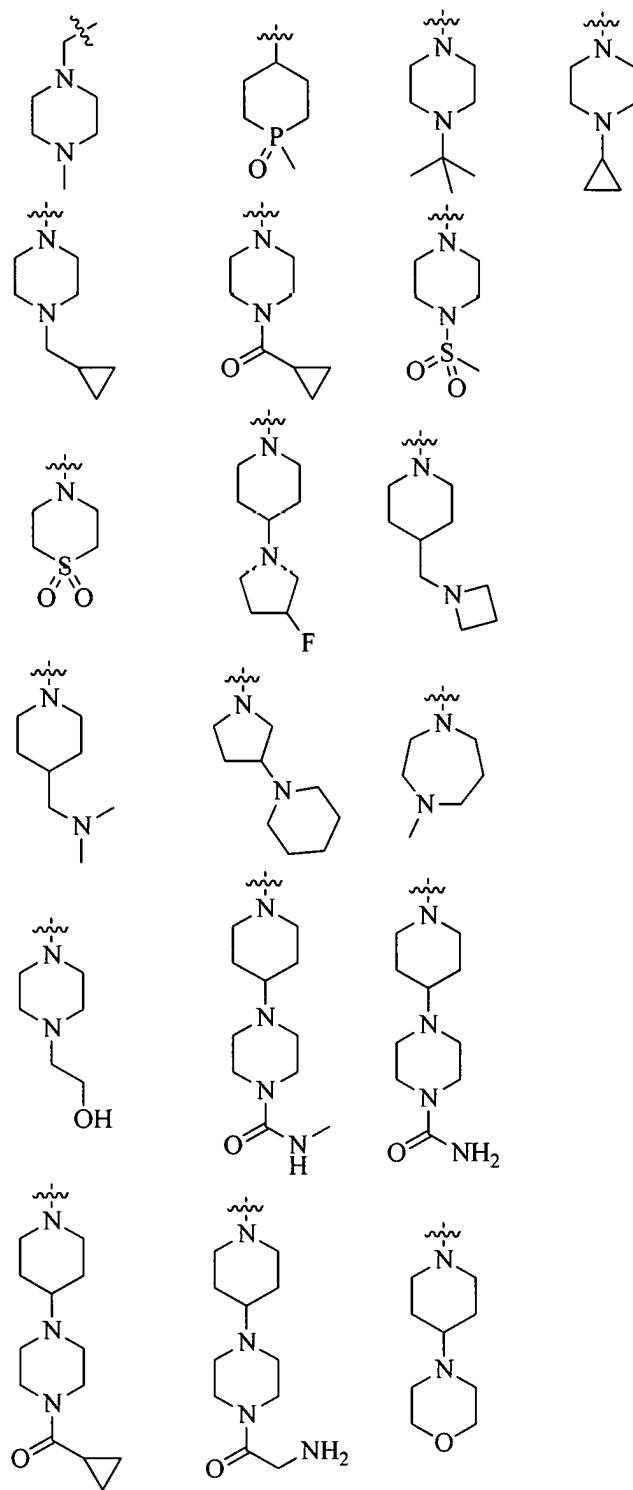
20. The compound of claim 12 in which at least one substituent **R^a** is a 5-, **6-** or 7-**membered heterocyclic** or 5- or 6-membered heteroaryl, **linked to Ring A** either **directly** or by an ether bond, and which may be **further substituted** with **1, 2 or 3 substituents** independently selected from halo, $-\text{CN}$, $-\text{NO}_2$, **$-\text{R}^1$** , $-\text{OR}^2$, $-\text{O}-\text{NR}^1\text{R}^2$, $-\text{NR}^1\text{R}^2$, $-\text{NR}^1-\text{NR}^1\text{R}^2$, $-\text{NR}^1-\text{OR}^2$, $-\text{C}(\text{O})\text{YR}^2$, $-\text{OC}(\text{O})\text{YR}^2$, $-\text{NR}^1\text{C}(\text{O})\text{YR}^2$, $-\text{SC}(\text{O})\text{YR}^2$, $-\text{NR}^1\text{C}(=\text{S})\text{YR}^2$, $-\text{OC}(=\text{S})\text{YR}^2$, $-\text{C}(=\text{S})\text{YR}^2$, $-\text{YC}(=\text{NR}^1)\text{YR}^2$, $-\text{YC}(=\text{N}-\text{OR}^1)\text{YR}^2$, $-\text{YC}(=\text{N}-\text{NR}^1\text{R}^2)\text{YR}^2$, $-\text{YP}(=\text{O})(\text{YR}^3)(\text{YR}^3)$, $-\text{Si}(\text{R}^{3a})_3$, $-\text{NR}^1\text{SO}_2\text{R}^2$, $-\text{S}(\text{O})_r\text{R}^2$, $-\text{SO}_2\text{NR}^1\text{R}^2$ and $-\text{NR}^1\text{SO}_2\text{NR}^1\text{R}^2$; wherein each Y is independently a bond, $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^1-$.

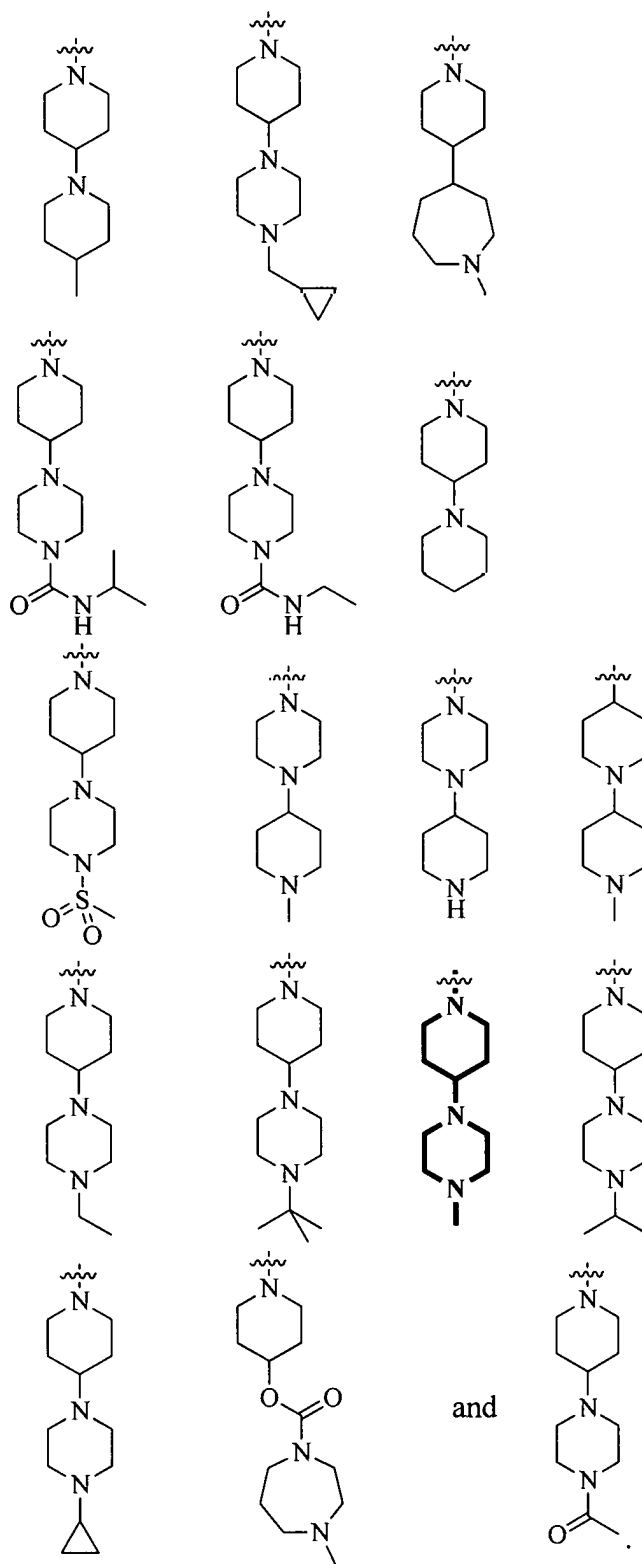
Claim 20 depends from claim 12, which reads on the approved product. The required variables and values from claim 20 to read on the approved product are highlighted in bold in the claim above. Thus, claim 20 claims the approved product.

Claim 24

24. The compound of any of claim 7, 18, 19, 20, or 21, in which the heterocyclic or heteroaryl **substituent R^a** is selected from the following:







Claim 24 depends from any of claims 7 and 18 to 21, of which claims 7 and 18 to 20 each read on the approved product. The required variable and value from claim 24 to read on

the approved product are highlighted in bold in the claim above. Thus, claim 24 claims the approved product.

Claim 26

26. The compound of claim 24 in which **L** is **NH**, **Ring E** is **aryl**, and each **R⁸** is independently selected from halo, **-R¹**, **-OR²**, **-S(O)₂R²** and **-P(=O)(R³)₂**.

Claim 26 depends from claim 24, which reads on the approved product. The required variables and values from claim 26 to read on the approved product are highlighted in bold in the claim above. Thus, claim 26 claims the approved product.

Claim 28

28. The compound of claim 26 in which **Ring E** contains **at least one R⁸** in the **ortho position**, relative to the ring atom attached to L.

Claim 28 depends from claim 26, which reads on the approved product. The required variable and value from claim 28 to read on the approved product are highlighted in bold in the claim above. Thus, claim 28 claims the approved product.

Claim 34

34. A pharmaceutical composition containing a compound of claim 24 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

Claim 34 depends from claim 24, which reads on the approved product. In addition to the active ingredient brigatinib, the approved product also comprises inactive ingredients, including lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica, each of which is a pharmaceutically acceptable vehicle. Thus, claim 34 claims the approved product.

Claim 36

36. A pharmaceutical composition containing a compound of claim 26 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

Claim 36 depends from claim 26, which reads on the approved product. In addition to the active ingredient brigatinib, the approved product also comprises inactive ingredients, including lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica, each of which is a pharmaceutically acceptable vehicle. Thus, claim 36 claims the approved product.

Claim 40

40. The compound of claim 1 selected from the following:
 5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;
 5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[4-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine;
 5-chloro-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N²-[5-(propan-2-yl)-1,3-oxazol-2-yl]pyrimidine-2,4-diamine;
 5-chloro-N²-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidine-2,4-diamine;
 N²-[5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-yl]-5-chloro-N⁴-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]pyrimidine-2,4-diamine;
 5-chloro-N⁴-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N²-{5-[4-(pyridin-2-yl)piperazin-1-yl]-1,3,4-oxadiazol-2-yl}pyrimidine-2,4-diamine;
 5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;
 5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidine-2,4-diamine;
 5-chloro-N²-(2-cyclopropyl-1,3-oxazol-5-yl)-N⁴-[4-(diethylphosphoryl)-2-methoxyphenyl]pyrimidine-2,4-diamine;
 N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-4,6-diamine;
 6-chloro-N⁵-[4-(dimethylphosphoryl)phenyl]-N'-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}-1,2,4-triazine-3,5-diamine;
 N⁵-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-[4(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine; and,

5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;
or a pharmaceutically acceptable salt thereof.

As highlighted above in bold, claim 40 specifically claims, *inter alia*, 5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, which is brigatinib, the active ingredient of the approved product. Thus, claim 40 claims the approved product.

Claim 41

41. The compound of claim 1 selected from the following:
N⁴-(3,5-dimethylphenyl)-N²-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine;
5-chloro-N²-(4-(dimethylphosphoryl)-2-methoxyphenyl)-N⁴-phenylpyrimidine-2,4-diamine;
N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine;
5-chloro-N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-chloro-N²-[4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;
N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
N²-[4-(Dimethylphosphoryl)-2-methoxyphenyl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-Chloro-N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-Chloro-N²-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-Chloro-N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-Chloro-N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-Chloro-N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
5-Chloro-N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4,5-triamine;

N^2 -[2-methoxy-4-(4-oxido-1,4-azaphosphinan-4-yl)phenyl]- N^4 -
 [2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 N^2 -[4-(dimethylphosphoryl)-2-methoxyphenyl]- N^4 -[2-(propan-2-
 ylsulfonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine;
 5-chloro- N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-
 N^4 -[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-chloro- N^2 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-
 N^4 -[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-chloro- N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-
 N^4 -phenylpyrimidine-2,4-diamine;
 N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^4 -[2-
 (propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-
 diamine;
 N^2 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^4 -[2-
 (propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-
 diamine;
 5-chloro- N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-
 N^4 -[4-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine;
 5-chloro- N^2 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-
 N^4 -[2-ethoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-
 yl]phenyl]pyrimidine-2,4-diamine;
 N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^4 -[2-
 (propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-methyl-
 N^4 -[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-chloro- N^4 -[2-methoxy-4-(4-methyl-4-oxido-1,4-
 azaphosphinan-1-yl)phenyl]- N^2 -[5-(propan-2-yl)-1,3-oxazol-2-
 yl]pyrimidine-2,4-diamine;
 5-chloro- N^2 -[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]- N^4 -[2-methoxy-
 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidine-
 2,4-diamine;
 N^2 -[5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-yl]-5-chloro- N^4 -
 [5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]pyrimidine-2,4-
 diamine;
 5-chloro- N^4 -[4-(dimethylphosphoryl)-2-(propan-2-
 ylsulfonyl)phenyl]- N^2 -{5-[4-(pyridin-2-yl)piperazin-1-yl]-1,3,4-
 oxadiazol-2-yl}pyrimidine-2,4-diamine-4;
 5-chloro- N^2 -(5-cyclopropyl-1,3-oxazol-2-yl)- N^4 -{2-methoxy-4-
 [4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-
 yl]phenyl}pyrimidine-2,4-diamine;
 5-chloro- N^2 -(5-cyclopropyl-1,3-oxazol-2-yl)- N^4 -[4-(1-ethyl-4-
 oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidine-
 2,4-diamine;
 5-chloro- N^2 -(2-cyclopropyl-1,3-oxazol-5-yl)- N^4 -[4-
 (diethylphosphoryl)-2-methoxyphenyl]pyrimidine-2,4-diamine;
 N-(3,5-dimethylphenyl)- N^4 -[4-
 (dimethylphosphoryl)phenyl]pyrimidine-4,6-diamine;

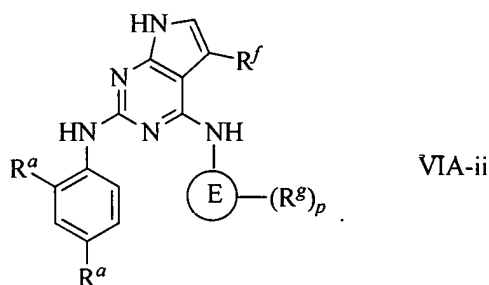
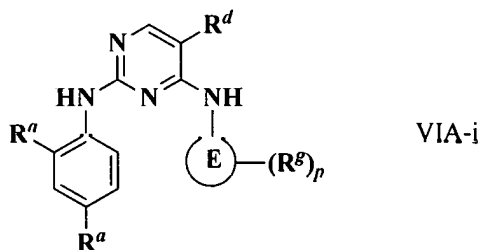
N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-2-methyl-N'-phenylpyrimidine-4,6-diamine;
 N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-[3-fluoro-5-(trifluoromethyl)phenoxy]pyridazin-3-amine;
 N-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine;
 N-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine;
 N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-4,6-diamine;
 N³-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N³-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N³-[4-(diethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 6-chloro-N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-phenyl-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;

6-chloro-N⁵-[4-(dimethylphosphoryl)phenyl]-N³-{2-methoxy-4-[4-(4-ethylpiperazin-1-yl)piperidin-1-yl]phenyl}-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 N⁵-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N³-{2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro-N³-[4-(diethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine; and
5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;
 or a pharmaceutically acceptable salt thereof.

As highlighted above in bold, claim 41 specifically claims, *inter alia*, 5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, which is brigatinib, the active ingredient of the approved product. Thus, claim 41 claims the approved product.

Claim 42

42. The compound of claim 1 of Formula VIA-i or Formula VIA-ii:



Claim 42 depends from claim 1, which reads on the approved product. The required variables and values from claim 42 to read on the approved product are highlighted in bold in the claim above. Thus, claim 42 claims the approved product.

Claim 43

43. The compound of claim 42 in which the **ortho** **R^a** is H, halo, C1-C4 alkyl, C1-C4 haloalkyl, **C1-C4 alkoxy**, C1-C4 haloalkoxy or -P(=O)(R³)₂.

Claim 43 depends from claim 42, which reads on the approved product. The required variable and value from claim 43 to read on the approved product are highlighted in bold in the claim above. Thus, claim 43 claims the approved product.

Claim 44

44. The compound of claim 42 in which **R^d** is F, **Cl**, C1-C4 alkyl, cyclopropyl, CF₃, OMe, or OCF₃, or **R^f** is H, -CH₃ or halo.

Claim 44 depends from claim 42, which reads on the approved product. The required variable and value from claim 44 to read on the approved product are highlighted in bold in the claim above. Thus, claim 44 claims the approved product.

Claim 45

45. The compound of claim 43 in which **R^d** is F, **Cl**, C1-C4 alkyl, cyclopropyl, CF₃, OMe, or OCF₃, or R^f is H, -CH₃ or halo.

Claim 45 depends from claim 43, which reads on the approved product. The required variable and value from claim 45 to read on the approved product are highlighted in bold in the claim above. Thus, claim 45 claims the approved product.

Claim 46

46. The compound of claim 42 in which **Ring E** is **aryl**, and each **R^g** is independently -SO₂CH₃, -SO₂-iPr, -SO₂NH-iPr, -SONH-nPr, -SO₂NEt₂, -**P(O)(CH₃)₂**, P(O)(Et)₂, -P(O)(Pr)₂, Me, OMe, -O-iPr, -OCF₃, CN, -C(O)CH₃, -C(O)NH₂, -C(O)NHCH₃, or, -C(O)NH-iPr.

Claim 46 depends from claim 42, which reads on the approved product. The required variables and values from claim 46 to read on the approved product are highlighted in bold in the claim above. Thus, claim 46 claims the approved product.

Claim 47

47. The compound of claim 43 in which **Ring E** is **aryl**, and each **R^g** is independently -SO₂CH₃, -SO₂-iPr, -SO₂NH-iPr, -SONH-nPr, -SO₂NEt₂, -**P(O)(CH₃)₂**, -P(O)(Et)₂, -P(O)(Pr)₂, Me, OMe, -OCF₃, CN, -C(O)CH₃, -C(O)NH₂, -C(O)NHCH₃, or, -C(O)NH-iPr.

Claim 47 depends from claim 43, which reads on the approved product. The required variables and values from claim 47 to read on the approved product are highlighted in bold in the claim above. Thus, claim 47 claims the approved product.

Claim 48

48. The compound of claim 44 in which **Ring E** is **aryl**, and each **R^g** is independently -SO₂CH₃, -SO₂-iPr, -SO₂NH-iPr, -SONH-nPr, -SO₂NEt₂, -**P(O)(CH₃)₂**, -P(O)(Et)₂, -P(O)(Pr)₂, Me, OMe, -OCF₃, CN, -C(O)CH₃, -C(O)NH₂, -C(O)NHCH₃, or, -C(O)NH-iPr.

Claim 48 depends from claim 44, which reads on the approved product. The required variables and values from claim 48 to read on the approved product are highlighted in bold in the claim above. Thus, claim 48 claims the approved product.

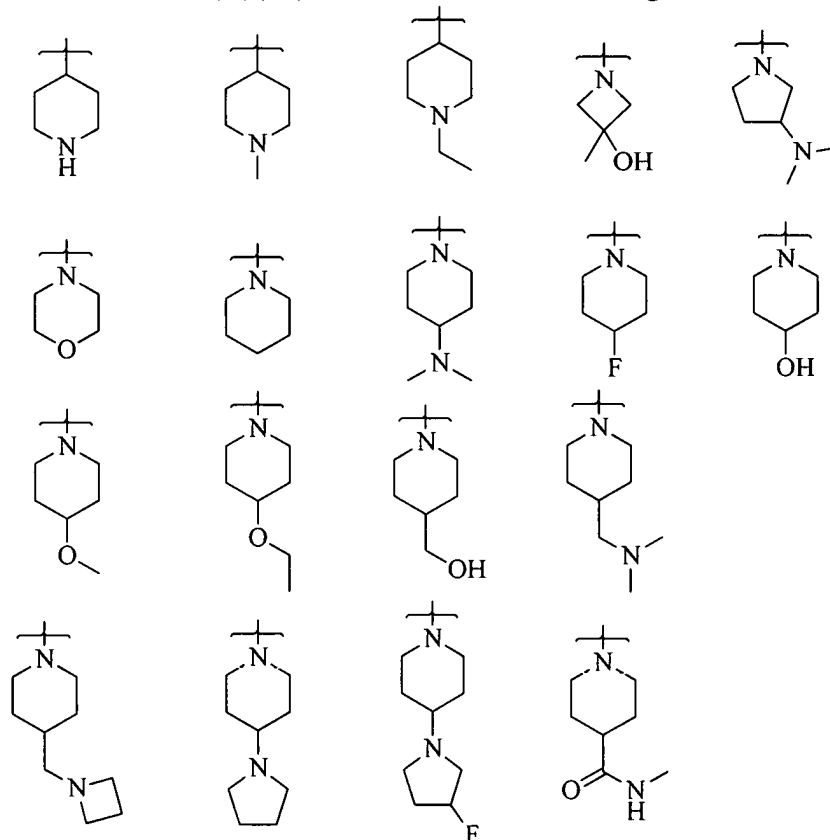
Claim 49

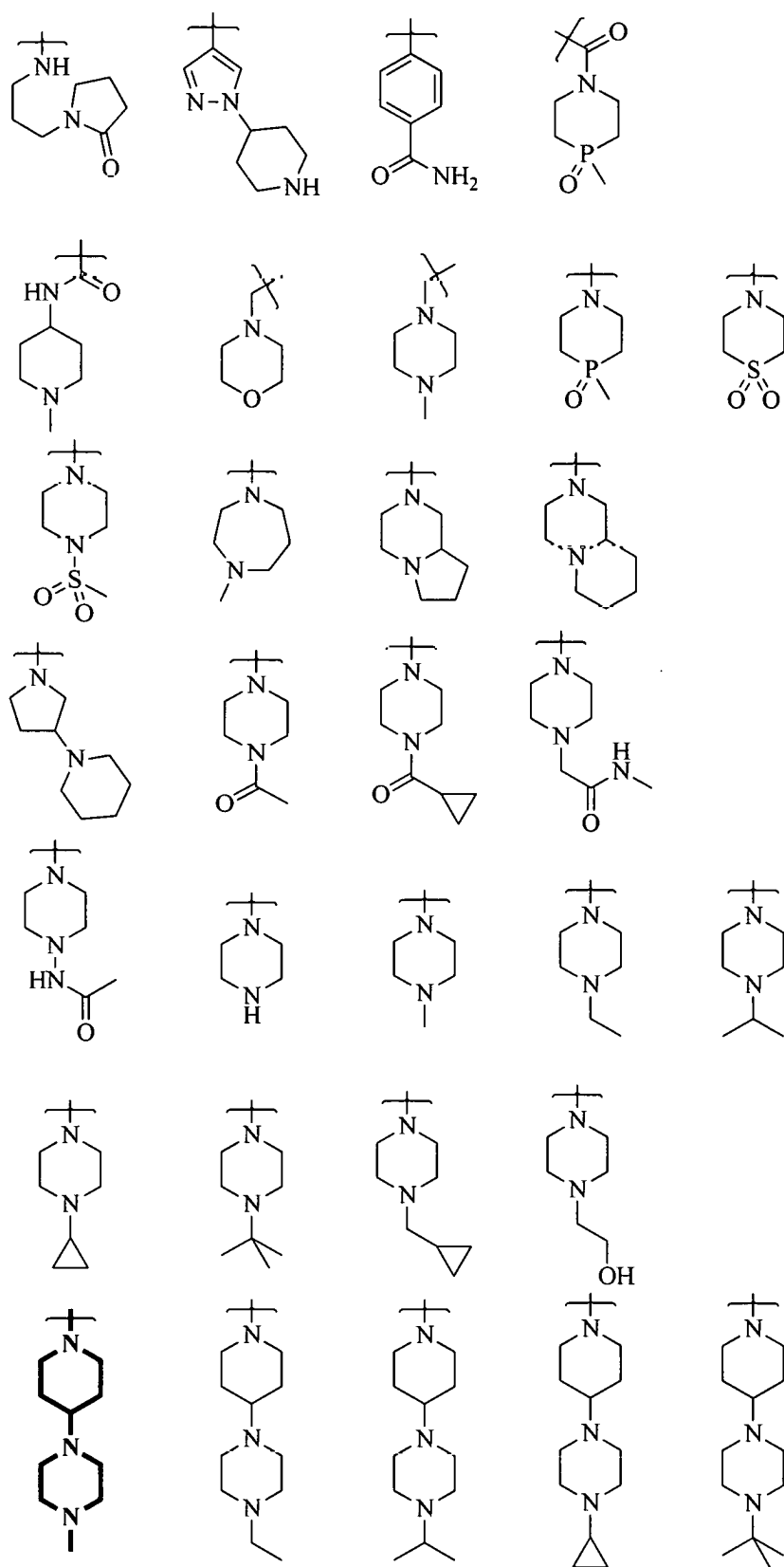
49. The compound of claim 45 in which **Ring E** is **aryl**, and each **R^g** is independently -SO₂CH₃, -SO₂-iPr, -SO₂NH-iPr, -SONH-nPr, -SO₂NEt₂, -**P(O)(CH₃)₂**, -P(O)(Et)₂, -P(O)(Pr)₂, Me, OMe, -O-iPr, -OCF₃, CN, -C(O)CH₃, -C(O)NH₂, -C(O)NHCH₃, or, -C(O)NH-iPr.

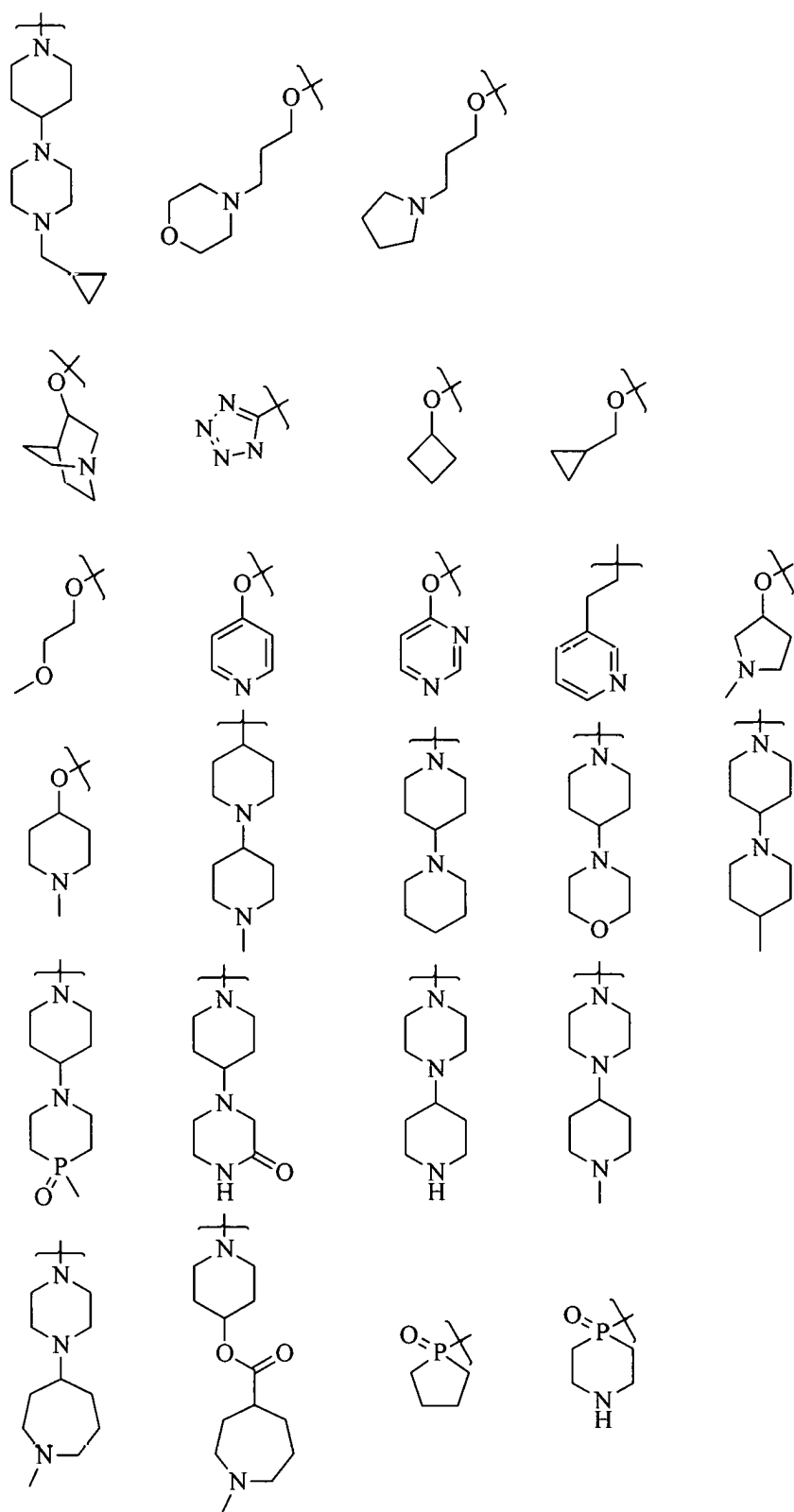
Claim 49 depends from claim 45, which reads on the approved product. The required variables and values from claim 49 to read on the approved product are highlighted in bold in the claim above. Thus, claim 49 claims the approved product.

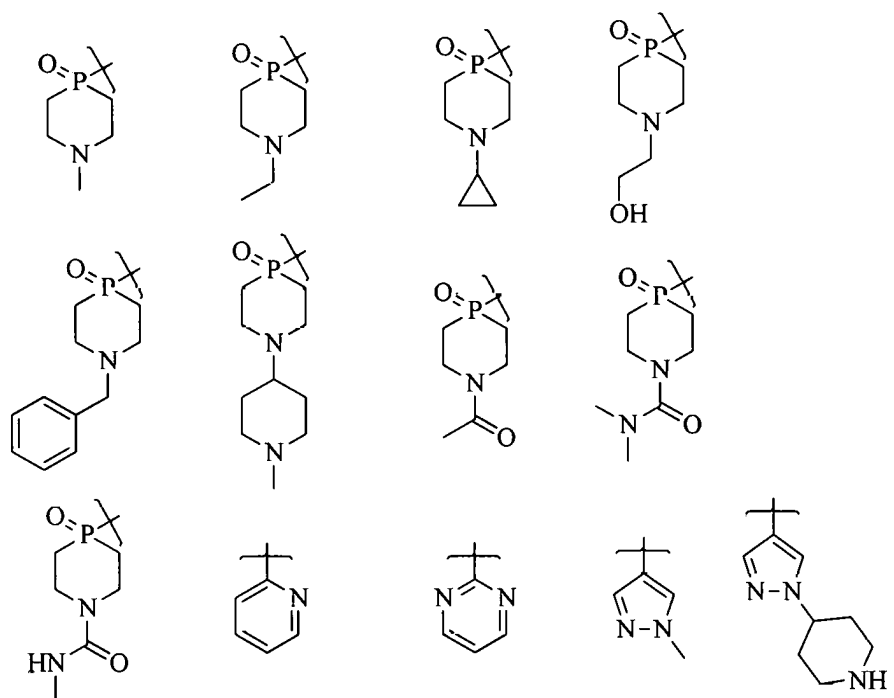
Claim 50

50. The compound of any of claim 42-45 or 47 in which the **para R^a** is or contains -P(O)(R³)₂ or is **one of the following**:





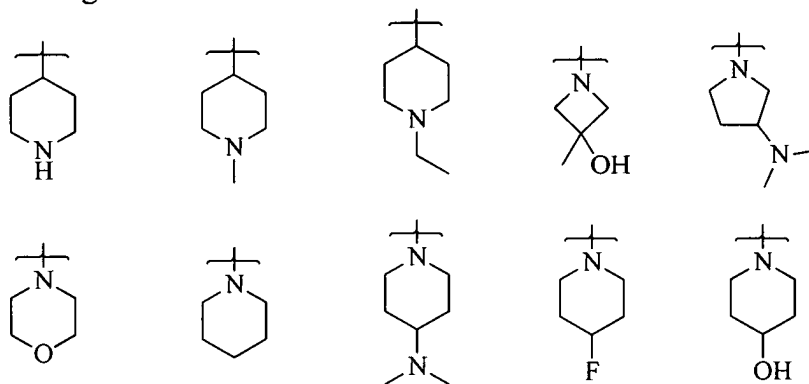


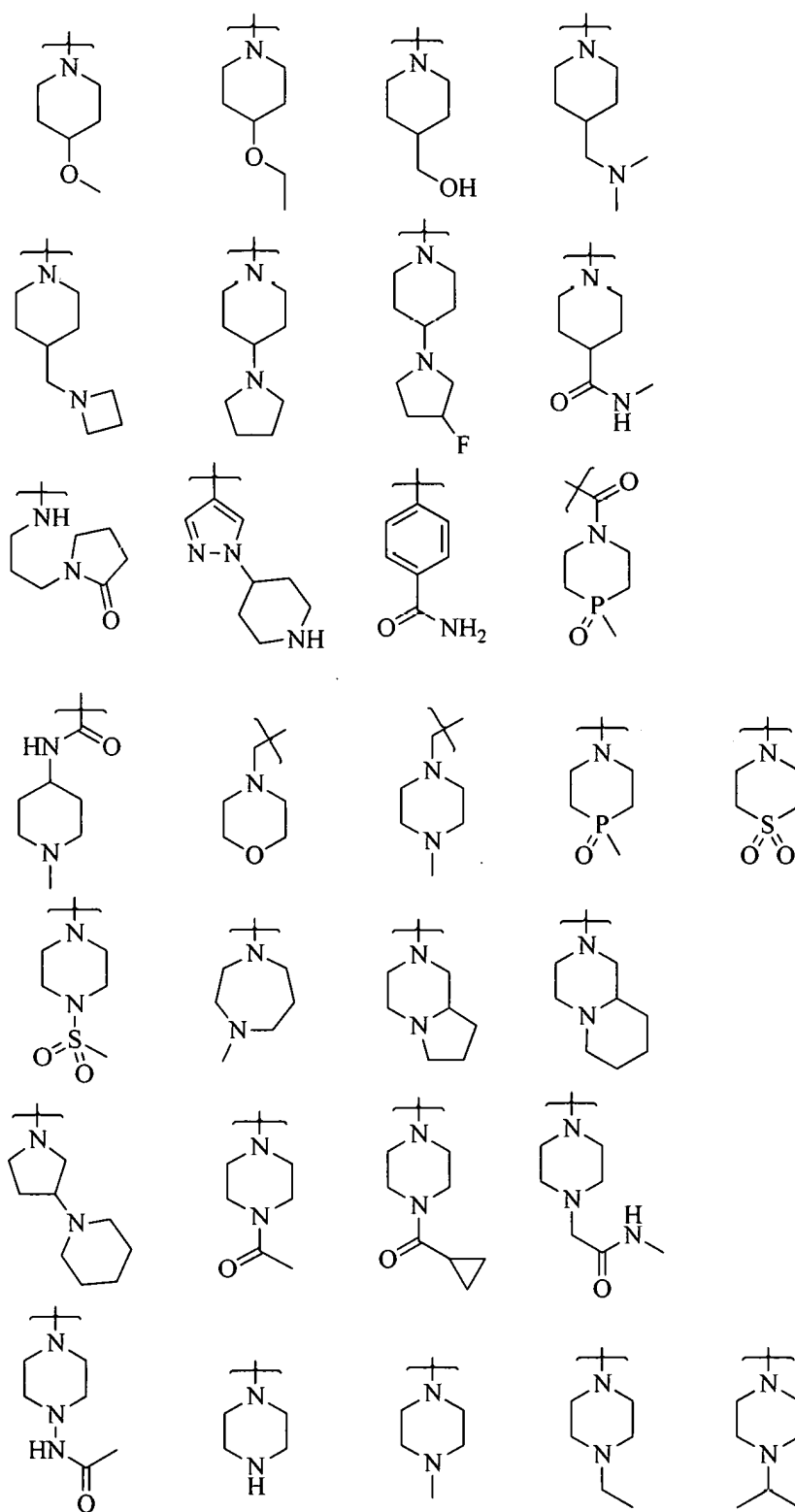


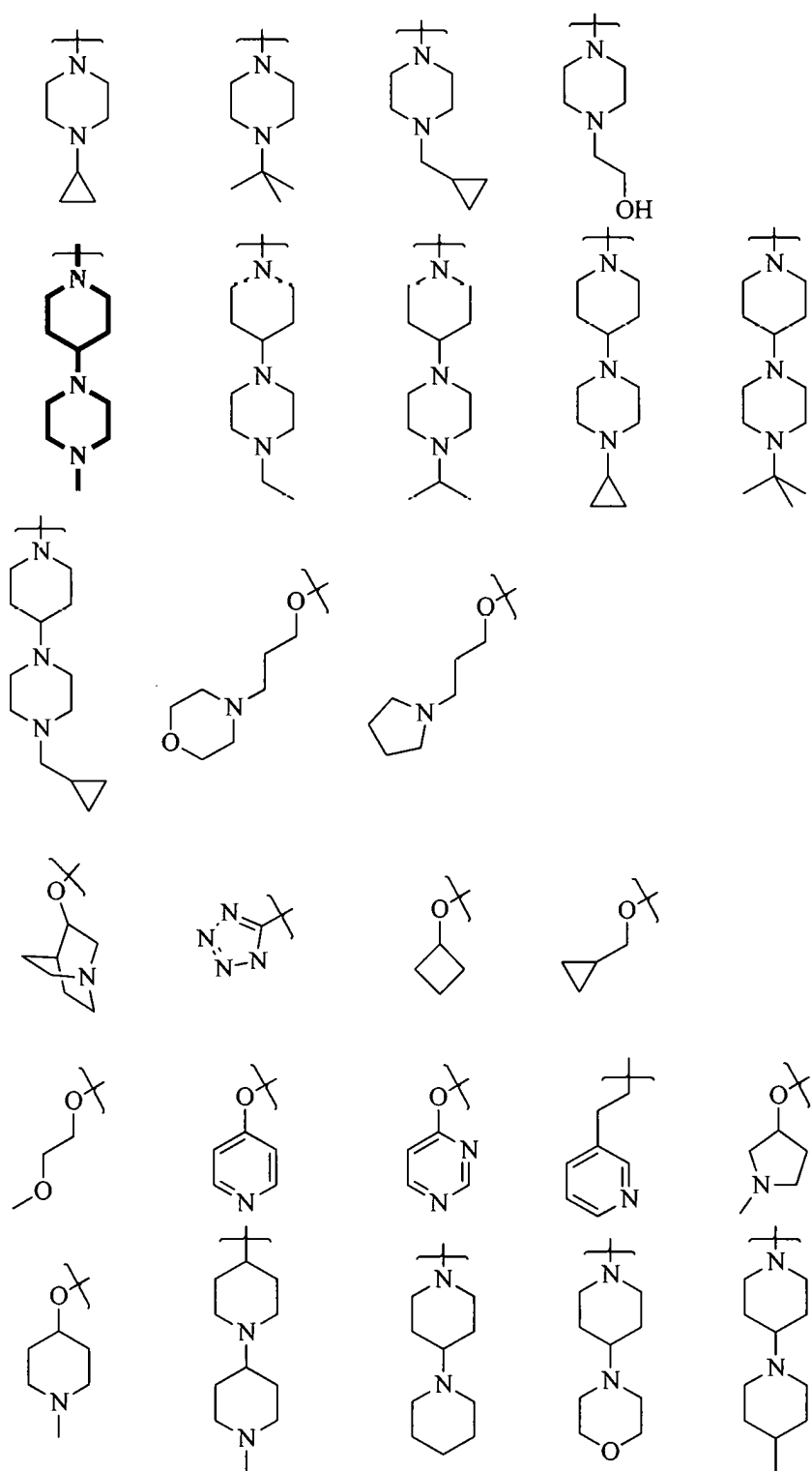
Claim 50 depends from claim any of 42 to 45 and 47, each of which reads on the approved product. The required variable and value from claim 50 to read on the approved product are highlighted in bold in the claim above. Thus, claim 50 claims the approved product.

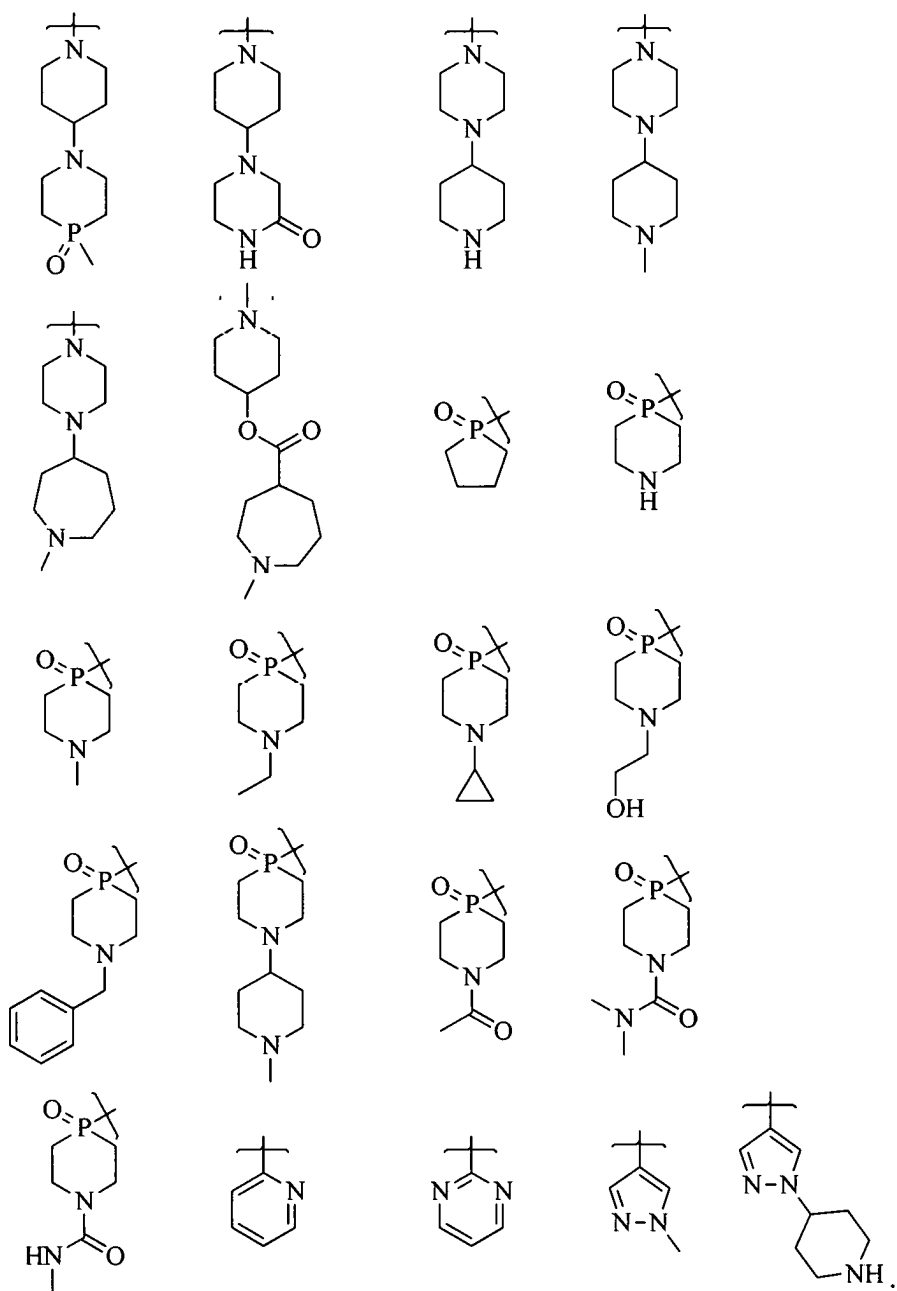
Claim 51

51. The compound of any of claim 42-45 or 47 in which at least one of R^g is or contains $-P(O)(R^3)_2$ and the **para** R^a one of the following:









Claim 51 depends from claim any of 42 to 45 and 47, each of which reads on the approved product. The required variable and value from claim 51 to read on the approved product are highlighted in bold in the claim above. Thus, claim 51 claims the approved product.

Claim 52

52. The compound of any of claims 1, 2, 3-7, 8 and 9-33 in which **L** is **NH**, **Ring E** is **aryl**, and each **R^g** is independently selected from halo, **-R¹**, **-OR²**, **-S(O),R²** and **-P(O)(R³)₂**.

Claim 52 depends from any of claims 1 to 33, of which 1 to 3, 5 to 7, 9 to 12, 15, 16, 18 to 20, 24, 26, and 28 each reads on the approved product. The required variables and values from claim 52 to read on the approved product are highlighted in bold in the claim above. Thus, claim 52 claims the approved product.

Claim 53

53. The compound of claim 52 in which **Ring E** contains at least one **R^g** in the **ortho position**, relative to the ring atom attached to L.

Claim 53 depends from claim 52, which reads on the approved product. The required variable and value from claim 53 to read on the approved product are highlighted in bold in the claim above. Thus, claim 53 claims the approved product.

Claim 56

56. The compound of claim 52 in which at least one **R^g** is **P(=O)(R³)₂**, and is **-P(=O)(CH₃)₂** or **-P(=O)(CH₂CH₃)₂**.

Claim 56 depends from claim 52, which reads on the approved product. The required variable and value from claim 56 to read on the approved product are highlighted in bold in the claim above. Thus, claim 56 claims the approved product.

Claim 57

57. The compound of claim 24 in which L is **NH**; **X¹** is **N**; **X³** is **CR^d**; **X⁴** is **CR^e**; **Ring A** is **aryl** and optionally contains up to **two** additional **R^a**; and **Ring E** is **aryl** and contains **1-3R^g**, one of which being an **ortho**, meta or para **-P(=O)(R³)₂**.

Claim 57 depends from claim 24, which reads on the approved product. The required variables and values from claim 57 to read on the approved product are highlighted in bold in the claim above. Thus, claim 57 claims the approved product.

Claim 58

58. The compound of claim 53 in which at least one **R^g** is **-P(=O)(R³)₂**, and **R³** is **-CH₃** or **-CH₂CH₃**.

Claim 58 depends from claim 53, which reads on the approved product. The required variables and values from claim 58 to read on the approved product are highlighted in bold in the claim above. Thus, claim 58 claims the approved product.

Claim 61

61. A pharmaceutical composition containing a compound of claim 52 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

Claim 61 depends from claim 52, which reads on the approved product. In addition to the active ingredient brigatinib, the approved product also comprises inactive ingredients, including lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica, each of which is a pharmaceutically acceptable vehicle. Thus, claim 61 claims the approved product.

Claim 62

62. A pharmaceutical composition containing a compound of claim 56 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

Claim 62 depends from claim 56, which reads on the approved product. In addition to the active ingredient brigatinib, the approved product also comprises inactive ingredients, including lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica, each of which is a pharmaceutically acceptable vehicle. Thus, claim 62 claims the approved product.

Claim 63

63. A pharmaceutical composition containing a compound of claim 58 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

Claim 63 depends from claim 58, which reads on the approved product. In addition to the active ingredient brigatinib, the approved product also comprises inactive ingredients, including lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica, each of which is a pharmaceutically acceptable vehicle. Thus, claim 63 claims the approved product.

Claim 66

66. A pharmaceutical composition containing a compound of any of claim 1, 2, 3-7, 8, 9, 23 or 38-41, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

Claim 66 depends from any of claims 1 to 23 and 38 to 41, of which 1-3, 5-7, 9-12, 15, 16, 18 to 20, 40, and 41 each reads on the approved product. In addition to the active ingredient brigatinib, the approved product also comprises inactive ingredients, including lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica, each of which is a pharmaceutically acceptable vehicle. Thus, claim 66 claims the approved product.

Claim 72

72. The compound of claim 40, wherein the compound is 5-chloro- N^4 -[2-(dimethylphosphoryl)phenyl]- N^2 -{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

Claim 72 specifically claims 5-chloro- N^4 -[2-(dimethylphosphoryl)phenyl]- N^2 -{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, which is brigatinib, the active ingredient of the approved product. Thus, claim 72 claims the approved product.

Thus, claims 1 to 3, 5 to 7, 9 to 12, 15, 16, 18 to 20, 24, 26, 28, 34, 36, 40 to 53, 56 to 58, 61 to 63, 66, and 72 of the '462 Patent each read on the approved product.

(10) *“A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:*

(i) *For a patent claiming a human drug, antibiotic, or human biological product:*

(A) *The effective date of the investigational new drug (IND) application and the IND number;*

(B) *The date on which a new drug application (NDA) or a Produce License Application (PLA) was initially submitted and the NDA or PLA number; and*

(C) *The date on which the NDA was approved or the Product License issued”*

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for ALUNBRIG™ are as follows:

(A) Investigational new drug (“IND”) application number 110,935 became effective on July 26, 2011. Exhibit J (Compendium of Significant Regulatory Activities in Connection with ALUNBRIG™).

(B) The new drug application (“NDA”) was submitted on August 29, 2016, and was later assigned NDA number 208772. Exhibit B.

(C) NDA number 208772 was approved by FDA on April 28, 2017. Exhibit B.

- (11) *“A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities”*

Exhibit J is attached hereto to briefly describe significant activities undertaken with respect to the approval of ALUNBRIG™ during the applicable regulatory review period and the dates applicable to such activities.

- (12) *“A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined”*

Based on the current determination of 626 days of PTA (Exhibits D & F), Applicant is of the opinion that the '462 patent is eligible for an extension of **81 days**.

A. Eligibility:

- (a) Pursuant to 35 U.S.C. § 156(a), the '462 patent claims, *inter alia*, the approved product;
- (b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '462 patent has not expired before submission of this application for extension;
- (c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '462 patent has never been extended;
- (d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owner of record of the '462 patent;
- (e) Pursuant to 35 U.S.C. § 156(a)(4), the product, ALUNBRIG™, has been subject to a regulatory review period before its commercial marketing or use;
- (f) Pursuant to 35 U.S.C. § 156(a)(5), the permission for the commercial marketing or use of ALUNBRIG™ after the regulatory review period is the first permitted commercial marketing or use of the product;
- (g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product ALUNBRIG™.

B. Regulatory Review Period:

- (a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from July 26, 2011 (the date IND application number 110,935 became effective) to August 29, 2016 (the date the NDA was initially submitted) is 1,862 days. Accordingly, Applicant calculates the “Testing Phase” as 1,862 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from August 29, 2016 (the date the NDA was initially submitted) to April 28, 2017 (the date of NDA approval) is 243 days. Accordingly, Applicant calculates the “Approval Phase” as 243 days.

C. Extended Patent Term:

(a) The number of days in the Testing Phase which were on and before April 21, 2015, the date on which the '462 Patent issued, is 1,366 days. Accordingly, 1,366 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the “Adjusted Testing Phase” to be 496 days. The number of days in the Approval Phase which were on and before April 21, 2015, the date on which the '462 Patent issued, is 0 days. Thus, Applicant calculates the “Adjusted Approval Phase” to be 243 days.

(b) As demonstrated in Exhibit J, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 248 days. Accordingly, 248 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii). Thus, Applicant calculates the regulatory review period to be 491 days (496 days minus 248 days plus 243 days). This regulatory review period is subject to reductions as explained below.

(d) The date that is 491 days from the expiration date of the '426 Patent is June 11, 2032 (the '426 Patent is currently set to expire February 6, 2031). The date that is 14 years from the date of approval of ALUNBRIG™ is April 28, 2031. Accordingly, the fourteen year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) should operate to reduce the period of extension by 410 days, that is, from June 11, 2032 (*i.e.*, the expiration date of the '426 Patent plus the period of extension) to April 28, 2031 (*i.e.*, the date that is fourteen years after the date of approval of ALUNBRIG™ on April 28, 2017). Accordingly, the period of extension of 491 days subject to the fourteen year limitation should be **81** days (491 days minus 410 days).

(e) The period of extension (81 days) is less than five (5) years.

Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

Alternatively, based on the request to adjust the PTA from 626 days to 591 days (Exhibit G), Applicant is of the opinion that the '462 patent is eligible for an extension of 116 days.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '462 patent claims, *inter alia*, the approved product;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '462 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '462 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owner of record of the '462 patent;

(e) Pursuant to 35 U.S.C. § 156(a)(4), the product, ALUNBRIG™, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. § 156(a)(5), the permission for the commercial marketing or use of ALUNBRIG™ after the regulatory review period is the first permitted commercial marketing or use of the product;

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product ALUNBRIG™.

B. Regulatory Review Period:

(a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from July 26, 2011 (the date IND application number 110,935 became effective) to August 29, 2016 (the date the NDA was initially submitted) is 1,862 days. Accordingly, Applicant calculates the "Testing Phase"

as 1,862 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from August 29, 2016 (the date the NDA was initially submitted) to April 28, 2017 (the date of NDA approval) is 243 days. Accordingly, Applicant calculates the “Approval Phase” as 243 days.

C. Extended Patent Term:

(a) The number of days in the Testing Phase which were on and before April 21, 2015, the date on which the '462 Patent issued, is 1,366 days. Accordingly, 1,366 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the “Adjusted Testing Phase” to be 496 days. The number of days in the Approval Phase which were on and before April 21, 2015, the date on which the '462 Patent issued, is 0 days. Thus, Applicant calculates the “Adjusted Approval Phase” to be 243 days.

(b) As demonstrated in Exhibit J, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 248 days. Accordingly, 248 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii). Thus, Applicant calculates the regulatory review period to be 491 days (496 days minus 248 days plus 243 days). This regulatory review period is subject to reductions as explained below.

(d) The date that is 491 days from the expiration date of the '426 Patent is May 7, 2032 (the '426 Patent would be set to expire January 2, 2031 if the PTA is adjusted to 591 days as requested (Exhibit G)). The date that is 14 years from the date of approval of ALUNBRIG™ is April 28, 2031. Accordingly, the fourteen year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) should operate to reduce the period of extension by 375 days, that is, from May 7, 2032 (*i.e.*, the expiration date of the '426 Patent plus the period of extension) to April 28, 2031 (*i.e.*, the date that is fourteen years after the date of approval of ALUNBRIG™ on April 28, 2017). Accordingly, the period of extension of 491 days subject to the fourteen

year limitation should be **116** days (491 days minus 375 days).

(e) The period of extension (116 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

- (13) *"A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought"*

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

- (14) *"The prescribed fee for receiving and acting upon the application for extension"*

The prescribed fee for receiving and acting upon this application is \$1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). The Director is authorized to charge this fee and any additional fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013.

- (15) *"The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed"*

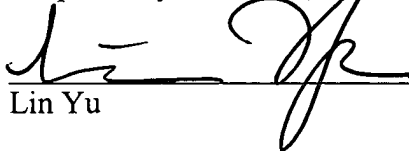
Please direct all inquiries and correspondence relating to this application to:

Dale L. Rieger, Ph.D., Esq.
JONES DAY
250 Vesey Street
New York, NY 10281-1047
Tel: (858) 314-1130
Fax: (858) 314-1150

- (16) Pursuant to 37 C.F.R. § 1.740(b), this Application is accompanied by two additional copies of such application for a total of three copies.

Date: June 21, 2017

Respectfully submitted,


Lin Yu

57,083

Reg. No.

For: Dale Rieger

43,045

JONES DAY
250 Vesey Street
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EXHIBIT A

J:DAVID L. BERSTEIN COMPANY:ARIAD PHARMACEUTICALS INC.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

OCTOBER 21, 2011

PTAS

DAVID L. BERSTEIN
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UNITED STATES PATENT AND TRADEMARK OFFICE
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RECORDATION DATE: 10/18/2011

REEL/FRAME: 027097/0423
NUMBER OF PAGES: 21

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

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DOC DATE: 06/09/2011

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DOC DATE: 06/13/2011

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027097/0423 PAGE 2

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DOC DATE: 04/29/2011

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APPLICATION NUMBER: 12736910

FILING DATE:

PATENT NUMBER:

ISSUE DATE:

TITLE: PHOSPHORUS DERIVATIVES AS KINASE INHIBITORS

MARY BENTON, EXAMINER
ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

D:DAVID L. BERSTEIN COMPANY:ARIAD PHARMACEUTICALS INC.

10/18/2011 16:14 FAX 617 494 0208

ARIAD Pharmaceuticals

002

Form PTO 1595		10/18/2011 700473446		US Dept. of Commerce United States Patent and Trademark Office	
RECORDATION FORM COVER SHEET					
PATENTS ONLY					
To the Director of the U.S. Patent and Trademark Office: Please record the attached original documents or copies thereof.					
1. Name of conveying party(ies): Yihan Wang Wei-Sheng Huang Shuangying Liu William C. Shakespeare R. Mathew Thomas Jiwei Qi Feng Li Xiaotian Zhu Anna Kohlmann David C. Dalgarno Jan Antoinette C. Romero Dong Zou			2. Name and address of receiving party(ies): Name: <u>ARIAD Pharmaceuticals, Inc.</u> Internal Address: <u>26 Landsdowne Street</u> Street Address: <u>26 Landsdowne Street</u> City: <u>Cambridge</u> State: <u>MA</u> Zip: <u>02139</u> Country: <u>USA</u> Additional names attached? ☐ Yes ☒ No		
Additional name(s) of conveying parties attached? ☐ Yes ☒ No					
3. Nature of conveyance/Execution Date(s): Execution Date(s): <u>Jun 20, 2011, June 9, 2011, December 4, 2000, June 13, 2011, June 10, 2011, June 10, 2011, June 9, 2011, June 9, 2011, February 25, 2011, June 9, 2011, June 29, 2011, April 29, 2011</u> ☒ Assignment ☐ Merger ☐ Security Agreement ☐ Change of Name ☐ Other _____					
4. Application or patent number(s): A. Patent Application No.(s) <u>12/736,910</u>			☐ This document is being filed together with a new application. B. Patent No.(s) Additional numbers attached? ☐ Yes ☒ No		
5. Name and address to whom correspondence concerning document should be mailed: Name: <u>David L. Bernstein</u> Internal Address: <u>ARIAD Pharmaceuticals Inc.</u> Street Address: <u>26 Landsdowne Street</u> City: <u>Cambridge</u> State: <u>MA</u> Zip: <u>02139</u> Country: <u>USA</u> Phone Number: <u>617-494-0400</u> Fax Number: <u>617-494-0208</u>			6. Total number of applications and patents involved: _____ 7. Total fee (37 CFR 1.21(h) & 3.41) \$ <u>40.00</u> ☒ Authorized to be charged to Deposit Account No. <u>01-2315</u> 8. Payment Information Deposit Account Number: <u>01-2315</u> Authorized User Name: <u>David L. Bernstein</u>		
9. Signature: <u>David L. Bernstein</u> David L. Bernstein			October 18, 2011 Date		
Reg. No.: 31,235 Total number of pages including cover sheet, attachments and documents: <u>21</u>					
Documents to be recorded (including cover sheet) should be faxed to (571) 273-0140, or mailed to: Mail Stop Assignment Recordation Services, Director of the USPTO, PO Box 1450, Alexandria, VA 22313-1450					

[CH \$40.00] 012315 2736910

ASSIGNMENT

We, Yihan Wang of 45 Madison Avenue, Newton, MA, 02460; Wei-Sheng Huang of 8 Mohegan Road, Acton, MA, 01720; Shuangying Liu of 4 Cedar Street, #504, Wellesley, MA, 02481; William C. Shakespeare of 2 Hubley Lane, Southborough, MA, 01772; R. Mathew Thomas of 419 Massapoag Avenue, Sharon, MA, 02067; Jiwei Qi of 1 Autumn Street, West Roxbury, MA, 02132; Feng Li of 7 New Meadows Road, Winchester, MA, 01890; Xiaotian Zhu of 137 Temple Street, Newton, MA, 02465; Anna Kohlmann of 58 Thornberry Road, Winchester, MA, 01890; David C. Dalgarno of 50 Crowninshield Road, Brookline, MA, 02446; Jan Antoinette C. Romero of 33 Newbury Street, #2, Somerville, MA, 02144; and Dong Zou of 41 Sydney Lane, Concord, MA, 01742; in consideration of good and valuable consideration paid to us by ARIAD Pharmaceuticals, Inc., a corporation of the state of Delaware, having its principal place of business at 26 Landsdowne Street, Cambridge, MA 02139, the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said

ARIAD Pharmaceuticals, Inc.

Its successors and assigns, the entire interest for the United States of America and all foreign countries, including rights of priority under the international convention for the protection of industrial property in a certain invention relating to

Phosphorous Derivatives as Kinase Inhibitors

Described in patent application serial no. 12/736,910 filed on 22 November 2010 in the United States Patent and Trademark Office, and in all letters patent of the United States and all foreign countries which may or shall be granted on said invention, or any parts thereof, or on said application, or any divisional, continuing, reissue or other applications based in whole or in part thereon. And I agree, for myself and my executors and administrators, with said corporation and its successors and assigns, but at its or their expense and charges, hereafter to execute all applications, amended specifications, deed or other instrument, and to do all acts necessary or proper to secure the grant of letters patent in the United States and in all other countries to said corporation, with specifications and claims in such form as shall be approved by the counsel of said corporation and to vest and confirm in said corporation, its successors and assigns, the legal title to all such patents.

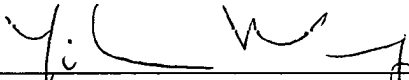
And we do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such letters patent as shall be granted upon said application or applications based thereon to said corporation, its successors and assigns.

USSN 12/736,910

Assignment

Page 2

Witness my hand this 20th day of June, 2011.

By: 
Yihan Wang

The above named Yihan Wang executed this document in my presence, this 20th day of June, 2011.


Witness signature

SUE WILSON
Witness name (please print)

Witness my hand this 9th day of June, 2011.

By: 
Wei-Sheng Huang

The above named Wei-Sheng Huang executed this document in my presence, this 9th day of June, 2011.


Witness signature

SUE WILSON
Witness name (please print)

USSN 12/736,910
Assignment
Page 3

Witness my hand this _____ day of _____, 2011.

By: _____
Shuangying Liu

The above named Shuangying Liu executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this 13th day of June, 2011.

By: William C. Shakespeare
William C. Shakespeare

The above named William C. Shakespeare executed this document in my presence, this 13th day of June, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

USSN 12/736,910

Assignment

Page 4

Witness my hand this 10th day of June, 2011.

By: R. Mathew Thomas
R. Mathew Thomas

The above named R. Mathew Thomas executed this document in my presence, this 10th day of June, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

Witness my hand this 10 day of June, 2011.

By: Jiwei Qi
Jiwei Qi

The above named Jiwei Qi executed this document in my presence, this 10th day of June, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

USSN 12/736,910

Assignment

Page 5

Witness my hand this 9 day of June, 2011.

By: Feng Li
Feng Li

The above named Feng Li executed this document in my presence, this 9th day of June, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

Witness my hand this 9th day of June, 2011.

By: Xiaotian Zhu
Xiaotian Zhu

The above named Xiaotian Zhu executed this document in my presence, this 9th day of June, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

USSN 12/736,910
Assignment
Page 6

Witness my hand this 25 day of February, 2011.

By: Anna Kohlmann
Anna Kohlmann

The above named Anna Kohlmann executed this document in my presence, this 25 day of February, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

Witness my hand this 9th day of June, 2011.

By: David C. Dalgarno
David C. Dalgarno

The above named David C. Dalgarno executed this document in my presence, this 9 day of June, 2011.

Sue Wilson
Witness signature

SUE WILSON
Witness name (please print)

USSN 12/736,910
Assignment
Page 7

Witness my hand this _____ day of _____, 2011.

By: _____
Jan Antoinette C. Romero

The above named Jan Antoinette C. Romero executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this 29 day of April, 2011.

By: _____
Dong Zou

The above named Dong Zou executed this document in my presence, this 29th day of April, 2011.

Witness signature

LATHA SWAMY
Witness name (please print)

ASSIGNMENT

We, Yihan Wang of 45 Madison Avenue, Newton, MA, 02460; Wei-Sheng Huang of 8 Mohegan Road, Acton, MA, 01720; Shuangying Lin of 4 Cedar Street, #504, Wellesley, MA, 02481; William C. Shakespeare of 2 Hubley Lane, Southborough, MA, 01772; R. Mathew Thomas of 419 Massapoag Avenue, Sharon, MA, 02067; Jiwei Qi of 1 Autumn Street, West Roxbury, MA, 02132; Feng Li of 7 New Meadows Road, Winchester, MA, 01890; Xiaotian Zhu of 137 Temple Street, Newton, MA, 02465; Anna Kohlmann of 58 Thornberry Road, Winchester, MA, 01890; David C. Dalgarno of 50 Crowninshield Road, Brookline, MA, 02446; Jan Antoinette C. Romero of 33 Newbury Street, #2, Somerville, MA, 02144; and Dong Zou of 41 Sydney Lane, Concord, MA, 01742; in consideration of good and valuable consideration paid to us by ARIAD Pharmaceuticals, Inc., a corporation of the state of Delaware, having its principal place of business at 26 Landsdowne Street, Cambridge, MA 02139, the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said

ARIAD Pharmaceuticals, Inc.

Its successors and assigns, the entire interest for the United States of America and all foreign countries, including rights of priority under the international convention for the protection of industrial property in a certain invention relating to

Phosphorous Derivatives as Kinase Inhibitors

Described in patent application serial no. 12/736,910 filed on 22 November 2010 in the United States Patent and Trademark Office, and in all letters patent of the United States and all foreign countries which may or shall be granted on said invention, or any parts thereof, or on said application, or any divisional, continuing, reissue or other applications based in whole or in part thereon. And I agree, for myself and my executors and administrators, with said corporation and its successors and assigns, but at its or their expense and charges, hereafter to execute all applications, amended specifications, deed or other instrument, and to do all acts necessary or proper to secure the grant of letters patent in the United States and in all other countries to said corporation, with specifications and claims in such form as shall be approved by the counsel of said corporation and to vest and confirm in said corporation, its successors and assigns, the legal title to all such patents.

And we do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such letters patent as shall be granted upon said application or applications based thereon to said corporation, its successors and assigns.

USSN 12/736,910

Assignment

Page 2

Witness my hand this _____ day of _____, 2011.

By: _____
Yihan Wang

The above named Yihan Wang executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this _____ day of _____, 2011.

By: _____
Wei-Sheng Huang

The above named Wei-Sheng Huang executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

USSN 12/736,910
Assignment
Page 3

Witness my hand this _____ day of _____, 2011.

By: _____
Shuangying Liu

The above named Shuangying Liu executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this _____ day of _____, 2011.

By: _____
William C. Shakespeare

The above named William C. Shakespeare executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

USSN 12/736,910
Assignment
Page 4

Witness my hand this _____ day of _____, 2011.

By: _____
R. Mathew Thomas

The above named R. Mathew Thomas executed this document in my presence, this _____ day
of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this _____ day of _____, 2011.

By: _____
Jiwei Qi

The above named Jiwei Qi executed this document in my presence, this _____ day of
_____, 2011.

Witness signature

Witness name (please print)

USSN 12/736,910
Assignment
Page 5

Witness my hand this _____ day of _____, 2011.

By: _____
Feng Li

The above named Feng Li executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this _____ day of _____, 2011.

By: _____
Xiaotian Zhu

The above named Xiaotian Zhu executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

USSN 12/736,910
Assignment
Page 6

Witness my hand this _____ day of _____, 2011.

By: _____
Anna Kohlmann

The above named Anna Kohlmann executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

Witness my hand this _____ day of _____, 2011.

By: _____
David C. Dalgarno

The above named David C. Dalgarno executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)

USSN 12/736,910

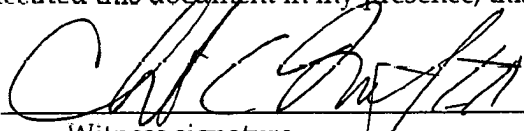
Assignment

Page 7

Witness my hand this 29 day of June, 2011.

By: 
Jan Antoinette C. Romero

The above named Jan Antoinette C. Romero executed this document in my presence, this 29 day of June, 2011.


Witness signature
Chester A Metcalf III
Witness name (please print)

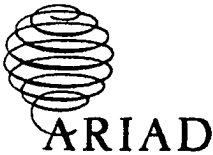
Witness my hand this _____ day of _____, 2011.

By: _____
Dong Zou

The above named Dong Zou executed this document in my presence, this _____ day of _____, 2011.

Witness signature

Witness name (please print)



**ARIAD PHARMACEUTICALS, INC.
AGREEMENT FOR NEW EMPLOYEES**

This Agreement, dated Dec 04, 2000 (the "Effective Date") is between ARIAD Pharmaceuticals, Inc., 26 Landsdowne Street, Cambridge, Massachusetts 02139 (the "Company"), and SHUANGYING LIU, of 1455 COMMONWEALTH AVE, #440, DORSET, MA 01919, an employee of the Company ("Employee").

BACKGROUND

The Employee has been employed by the Company to perform certain services for the Company. The employment by the Company of the Employee is contingent on the Employee first executing and delivering this Agreement to the Company. The Employee may be exposed to the Inventions and/or Proprietary Information (as defined below) of the Company. In consideration of the Company's employment of the Employee and for other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties covenant and agree as follows:

DEFINITIONS

1. As used in this Agreement, the terms "Field of Interest", "Proprietary Information", "Inventions", and "Business Associates" are defined as set forth below:

1.1

[REDACTED]

1.2

[REDACTED]

- 1.3 "Inventions" shall mean all inventions, improvements, materials, articles, equipment, processes, designs and techniques, whether or not patentable, and writings able to be protected by copyright, made or conceived or reduced to practice or learned by the Employee or by other employees, contractors, consultants, agents, Business Associates (as defined below) or others, either alone or jointly with others, which:

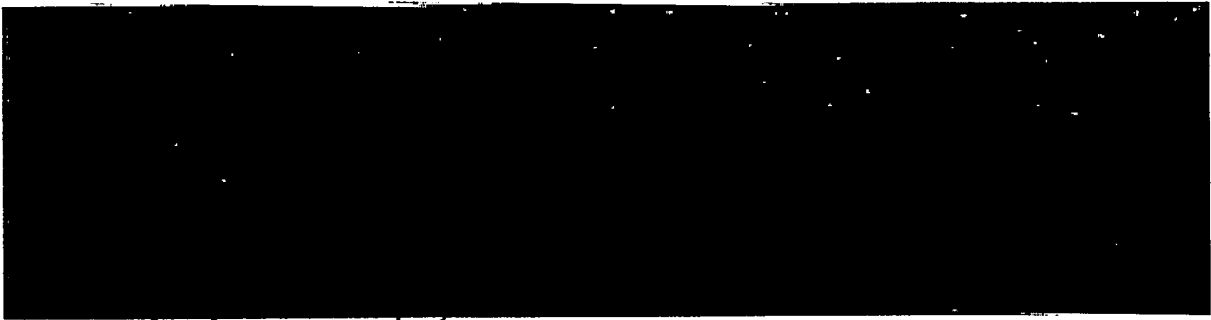
- relate to or arise out of the Employee's employment with the Company,
- relate to or are used in the business of the Company,
- result from tasks assigned to the Employee by the Company,
- result from use of premises or other facilities, equipment or services owned, leased or contracted for by the Company, or
- relate to the Company's Field of Interest.

1.4

[REDACTED]

PROPRIETARY INFORMATION AND INVENTIONS

2.



3. The Employee and the Company agree that:

3.1



3.2 All Inventions shall be the property of the Company.

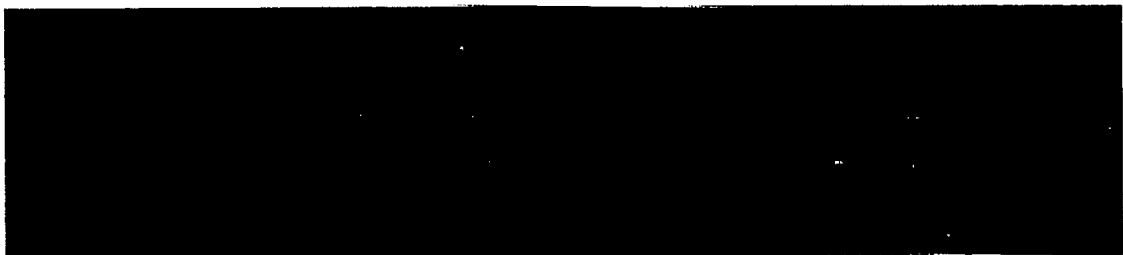
3.3



3.4



3.5



3.6 All patents, copyrights and other rights in connection therewith obtained or obtainable on any Inventions or Proprietary Information, including without limitation priority rights under international conventions for protection of intellectual property, shall be the property of the Company. The Employee hereby assigns to the Company any rights the Employee may have or acquire in any Inventions and/or Proprietary Information. The Employee further agrees to assist the Company in every reasonable manner to obtain, and from time to time enforce, patents or other appropriate protection of any Proprietary Information and any Inventions, as determined by the Company, in any and all countries. The Employee will execute and deliver to the Company all documents for use in applying for and obtaining such patents or other applicable protection thereon and enforcing the same, at the Company's request, together with any assignments thereof. The Company shall compensate the Employee at a reasonable rate for time actually spent and reasonable expenses actually incurred by the Employee, at the Company's request, on such assistance given after termination of the Employee's employment with the Company. The Employee hereby irrevocably designates the Company, with power of substitution, as the Employee's agent and attorney-in-fact to execute and file any such document and to do all lawful acts necessary to apply for and obtain patents and copyrights and to enforce the Company's rights under this Agreement.

3.7



[REDACTED]

4. The Employee has disclosed and described on Schedule A, attached to and made a part of this Agreement, all inventions and intellectual property which the Employee claims are the Employee's property, and which were conceived, discovered or made by the Employee solely or jointly with others prior to the Employee's employment by the Company. The absence of any such listing is a specific representation and warranty by the Employee that the Employee does not own any such invention or intellectual property.

[REDACTED]

5.

[REDACTED]

[REDACTED]

[REDACTED]

6.

[REDACTED]

6.1

[REDACTED]

6.2

[REDACTED]

6.3

[REDACTED]

7.

8.

9.

10. The Employee and the Company further agree that:

10.1 This Agreement will inure to the benefit of and be binding upon each of the parties hereto and their respective heirs, executors, administrators, representatives, successors and assigns.

10.2 The Employee's obligations under this Agreement shall survive the termination of the Employee's employment by the Company.

10.3 No waivers, express or implied, of any breach of this Agreement shall be held or construed as a waiver of any other breach of the same or any other covenant, agreement or duty hereunder.

10.4 This Agreement shall be construed and enforced in accordance with the law of the Commonwealth of Massachusetts. The parties stipulate to enforcement of this Agreement in any court having subject matter jurisdiction located in Eastern Massachusetts east of Worcester County at the initiative of either party, and each of the parties explicitly waives any otherwise applicable objection as to venue or personal jurisdiction affecting this choice.

10.5 This Agreement represents the entire agreement of the parties, and supersedes all previous agreements, if any, between the Employee and the Company with respect to the subject matter hereof, and may only be amended or modified by a written instrument signed by the parties.

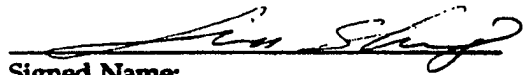
10.6 This Agreement does not provide for a specific term of employment or relate to compensation or benefits.

10.7 In the event that any one or more of the provisions contained in this Agreement shall for any reason be held to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability shall not affect any other provision of this Agreement, but this Agreement shall be construed as if such invalid, illegal or unenforceable provision had never been contained herein.

10.8 Any captions, headings and subheadings in this Agreement are for convenience only and are not a part of this Agreement and are not to be considered a part of this Agreement or to be used in determining the intent of the parties to this Agreement.

The parties have signed this Agreement under seal as of the Effective Date .

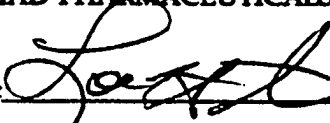
EMPLOYEE:



Signed Name:

ARIAD PHARMACEUTICALS, INC.

By:



Lee C. Steele
Senior Vice President
Chief Financial Officer

7458/NewEmp./Agree @QU/Apr'94

SCHEDULE A TO
AGREEMENT FOR NEW EMPLOYEES

The Employee represents and warrants that the following are the only inventions and intellectual property owned by the Employee pursuant to Paragraph 4 of the Agreement:

- ① "Synthesis, X-ray crystal-structure analysis, and NMR studies of $(\eta^3\text{-allyl})\text{palladium}(\text{II})$ complexes containing a novel dihydro(phosphinoaryl)oxazino ligand.
1. ~~Application in Palladium-catalyzed asymmetric synthesis.~~
- ② "Crystallographic studies of $\text{Cp}^*\text{-}1,5\text{-diacetylallyl}\}\text{-}\{2\text{-}(2'\text{-}(\text{diphenylphosphino})\text{phenyl})\text{-oxazoline-P,N}\}\text{palladium}(\text{II})$ hexafluorophosphate complexes complemented by $^1\text{H-NMR}$ investigations.
3. _____
4. _____
5. _____

Further details may be provided below.

EMPLOYEE:



DATE: Dec 04, 2000

EXHIBIT B



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208772

ACCELERATED APPROVAL

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M B A , R.A.C.
Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alunbrig (brigatinib) tablets, 30 and 90 mg.

This new drug application provides for the use of Alunbrig (brigatinib) tablets, 30 and 90 mg for treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)."

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208772.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

Based on the provided stability data, a 24-month expiration dating period is granted for 30 mg Alunbrig (brigatinib) tablets, and a 18-month expiration dating period is granted for 90 mg Alunbrig (brigatinib) tablets, from the date of manufacture of the tablets in the proposed commercial container closure systems when stored at USP controlled room temperature 20 to 25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F).

ADVISORY COMMITTEE

Your application for brigatinib was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in this intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submissions dated January 5, 2017 and March 28, 2017. This requirement, along with required completion dates, is listed below.

3190-1 Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of brigatinib in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

Trial Completion: March 2020
Final Report Submission: December 2020

We acknowledge submission of the protocol to IND 110935 on November 15, 2015. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of toxicity due to drug-drug interactions of Alunbrig (brigatinib) with inhibitors of CYP3A4.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

3190-2	Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib, to assess the potential for excessive drug toxicity.

The timetable you submitted on January 6, 2017 states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of a serious risk of toxicity from drug over-exposure due to the effect of impaired hepatic or renal function on the pharmacokinetics of Alunbrig (brigatinib).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3190-3 Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment.

The timetable you submitted on January 6, 2017 states that you will conduct this trial according to the following schedule:

Trial Completion: September 2017

Final Report Submission: June 2018

3190-4 Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment.

The timetable you submitted on January 6, 2017 states that you will conduct this trial according to the following schedule:

Trial Completion: March 2017 (completed)

Final Report Submission: September 2017

Submit clinical protocols to your IND 110935 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 3190-5 Submit the final analysis of intracranial response duration based upon independent radiology reviewer assessment of imaging data collected for two years following the date of enrollment of the last patient in Study AP26113-13-201.

The timetable you submitted on March 15, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion: September 2017
Final Report Submission: March 2018

- 3190-6 Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

The timetable you submitted on January 6, 2017, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2017

- 3190-7 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations.

The timetable you submitted on January 6, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: December 2017
Trial Completion: December 2019
Final Report Submission: June 2020

Submit clinical protocols to your IND 110935 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application within two weeks of receipt of this communication.

If you have any questions, call Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
04/28/2017

EXHIBIT C

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

ALUNBRIG™ (brigatinib) tablets, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

ALUNBRIG is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

DOSAGE AND ADMINISTRATION

90 mg orally once daily for the first 7 days; if tolerated, increase to 180 mg orally once daily. May be taken with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 30 mg and 90 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Occurred in 9.1% of patients at the recommended dose. Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment. Withhold ALUNBRIG for new or worsening respiratory symptoms and promptly evaluate for ILD/pneumonitis. Upon recovery, either dose reduce or permanently discontinue ALUNBRIG. (2.2, 5.1)
- **Hypertension:** Monitor blood pressure after 2 weeks and then at least monthly during treatment. For severe hypertension, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.2, 5.2)
- **Bradycardia:** Monitor heart rate and blood pressure regularly during treatment. If symptomatic, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.2, 5.3)

- **Visual Disturbance:** Advise patients to report visual symptoms. Withhold ALUNBRIG and obtain ophthalmologic evaluation, then dose reduce or permanently discontinue ALUNBRIG. (2.2, 5.4)
- **Creatine Phosphokinase (CPK) Elevation:** Monitor CPK levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.2, 5.5)
- **Pancreatic Enzyme Elevation:** Monitor lipase and amylase levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.2, 5.6)
- **Hyperglycemia:** Assess fasting serum glucose prior to starting ALUNBRIG and regularly during treatment. If not adequately controlled with optimal medical management, withhold ALUNBRIG, then consider dose reduction or permanently discontinue, based on severity. (2.2, 5.7)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use a non-hormonal method of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) with ALUNBRIG were nausea, diarrhea, fatigue, cough, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ARIAD Pharmaceuticals, Inc. at 1-844-217-6468 or www.alunbrig.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **CYP3A Inhibitors:** Avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG. (2.3, 7.1)
- **CYP3A Inducers:** Avoid concomitant use of ALUNBRIG with strong CYP3A inducers. (7.2)
- **CYP3A Substrates:** Hormonal contraceptives may be ineffective due to decreased exposure. (7.3)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosing regimen for ALUNBRIG is:

- 90 mg orally once daily for the first 7 days;
- if 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily.

Administer ALUNBRIG until disease progression or unacceptable toxicity.

If ALUNBRIG is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

ALUNBRIG may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets.

If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of ALUNBRIG at the scheduled time.

2.2 Dose Modifications for Adverse Reactions

ALUNBRIG dose modification levels are summarized in Table 1.

Table 1: Recommended ALUNBRIG Dose Reduction Levels

Dose	Dose Reduction Levels		
	First	Second	Third
90 mg once daily	60 mg once daily	permanently discontinue	N/A*
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

*Not applicable

Once reduced for adverse reactions, do not subsequently increase the dose of ALUNBRIG. Permanently discontinue ALUNBRIG if patients are unable to tolerate the 60 mg once daily dose.

Recommendations for dose modifications of ALUNBRIG for the management of adverse reactions are provided in Table 2.

Table 2: Recommended ALUNBRIG Dose Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
Interstitial Lung Disease (ILD) /Pneumonitis [see <i>Warnings and Precautions (5.1)</i>]	Grade 1	• If new pulmonary symptoms occur <u>during</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur <u>after</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 2	• If new pulmonary symptoms occur <u>during</u> the first 7 days

Adverse Reaction	Severity*	Dose Modification
		of treatment, withhold ALUNBRIG until recovery to baseline. Resume at next lower dose (Table 1) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur <u>after</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (Table 1); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 3 or 4	Permanently discontinue ALUNBRIG for ILD/pneumonitis.
Hypertension [see Warnings and Precautions (5.2)]	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy than previously used indicated)	• Withhold ALUNBRIG until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume ALUNBRIG at next lower dose (Table 1). • Recurrence: withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose (Table 1) <u>or</u> permanently discontinue treatment.
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	• Withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose (Table 1) <u>or</u> permanently discontinue treatment. • Recurrence: permanently discontinue ALUNBRIG for recurrence of Grade 4 hypertension.
Bradycardia (HR less than 60 bpm) [see Warnings and Precautions (5.3)]	Symptomatic bradycardia	• Withhold ALUNBRIG until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume ALUNBRIG at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• Permanently discontinue ALUNBRIG if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue ALUNBRIG.
Visual Disturbance [see Warnings and Precautions (5.4)]	Grade 2 or 3 visual disturbance	Withhold ALUNBRIG until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1).
	Grade 4 visual disturbance	Permanently discontinue ALUNBRIG.
Creatine	Grade 3 CPK elevation (greater	Withhold ALUNBRIG until recovery to Grade 1 or less (less

Adverse Reaction	Severity*	Dose Modification
Phosphokinase (CPK) Elevation [see Warnings and Precautions (5.5)]	than $5.0 \times \text{ULN}$	than or equal to $2.5 \times \text{ULN}$) or to baseline, then resume ALUNBRIG at same dose.
	Grade 4 CPK elevation (greater than $10.0 \times \text{ULN}$) or recurrence of Grade 3 elevation	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $2.5 \times \text{ULN}$) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
Lipase/Amylase Elevation [see Warnings and Precautions (5.6)]	Grade 3 lipase or amylase elevation (greater than $2.0 \times \text{ULN}$)	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times \text{ULN}$) or to baseline, then resume ALUNBRIG at same dose.
	Grade 4 lipase or amylase elevation (greater than $5.0 \times \text{ULN}$) or recurrence of Grade 3 elevation	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times \text{ULN}$) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
Hyperglycemia [see Warnings and Precautions (5.7)]	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reduction to the next dose (Table 1) <u>or</u> permanently discontinue ALUNBRIG.
Other	Grade 3	- Withhold ALUNBRIG until recovery to baseline, then resume at same dose. - Recurrence: withhold ALUNBRIG until recovery to baseline, then resume at next lower dose or discontinue ALUNBRIG (Table 1).
	Grade 4	- First occurrence: either withhold ALUNBRIG until recovery to baseline and resume at next lower dose (Table 1) <u>or</u> permanently discontinue. - Permanently discontinue ALUNBRIG for recurrence.
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

2.3 Dose Modification for Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors during treatment with ALUNBRIG [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, resume the ALUNBRIG dose that was tolerated prior to initiating the strong CYP3A inhibitor.

3 DOSAGE FORMS AND STRENGTHS

- 30 mg, round, white to off-white film-coated tablet with “U3” debossed on one side and plain on the other side
- 90 mg, oval, white to off-white film-coated tablet with “U7” debossed on one side and plain on the other side

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily).

Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction according to Table 1 after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.2 Hypertension

In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia [see *Warnings and Precautions* (5.3)].

5.3 Bradycardia

Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided [see *Warnings and Precautions* (5.2)].

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified [see *Dosage and Administration* (2.2)].

5.4 Visual Disturbance

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group.

Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.5 Creatine Phosphokinase (CPK) Elevation

In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.6 Pancreatic Enzyme Elevation

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.7 Hyperglycemia

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG as described in Table 1 or permanently discontinuing ALUNBRIG [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG [see *Use in Specific Populations* (8.1 and 8.3) and *Clinical Pharmacology* (12.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Interstitial Lung Disease (ILD)/Pneumonitis [see *Warnings and Precautions* (5.1)]
- Hypertension [see *Warnings and Precautions* (5.2)]
- Bradycardia [see *Warnings and Precautions* (5.3)]
- Visual Disturbance [see *Warnings and Precautions* (5.4)]
- Creatine Phosphokinase (CPK) Elevation [see *Warnings and Precautions* (5.5)]
- Pancreatic Enzyme Elevation [see *Warnings and Precautions* (5.6)]
- Hyperglycemia [see *Warnings and Precautions* (5.7)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least one dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90→180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90→180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to one year.

The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and brain metastases at baseline (69%) [see *Clinical Studies (14)*].

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90→180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90→180 mg group) and pneumonia (1.8% in the 90→180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90→180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90→180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Table 3: Adverse Reactions in $\geq 10\%$ (All Grades*) or $\geq 2\%$ (Grades 3-4) of Patients by Dose Group in ALTA (N=219)

Adverse Reactions	90 mg once daily N = 109		90→180 mg once daily N = 110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain [†]	17	0	10	0
General Disorders And Administration Site Conditions				
Fatigue [‡]	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
Respiratory, Thoracic And Mediastinal Disorders				
Cough	18	0	34	0
Dyspnea [§]	27	2.8	21	1.8 ^{‡‡}
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
Nervous System Disorders				
Headache [¶]	28	0	27	0.9
Peripheral Neuropathy [#]	13	0.9	13	1.8
Skin And Subcutaneous Tissue Disorders				
Rash [®]	15	1.8	24	3.6
Vascular Disorders				
Hypertension	11	5.5	21	6.4
Musculoskeletal And Connective Tissue Disorders				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgia ^{**}	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
Metabolism And Nutrition Disorders				
Decreased Appetite	22	0.9	15	0.9
Eye Disorders				
Visual Disturbance ^{††}	7.3	0	10	0.9
Infections				
Pneumonia	4.6	2.8 ^{‡‡}	10	5.5 ^{‡‡}
Psychiatric Disorders				
Insomnia	11	0	7.3	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

[†]Includes abdominal distension, abdominal pain, and epigastric discomfort

[‡]Includes asthenia and fatigue

[§]Includes dyspnea and exertional dyspnea

[¶]Includes headache and sinus headache

[#]Includes peripheral sensory neuropathy and paresthesia

[®]Includes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash

^{**}Includes musculoskeletal pain and myalgia

^{††}Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment

^{‡‡}Includes one Grade 5 event

Table 4: Laboratory Abnormalities in $\geq 20\%$ (All Grades*) of Patients by Regimen in ALTA (N=219)

Laboratory Abnormality	90 mg once daily N= 109		90→180 mg once daily N=110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia [†]	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6
Prolonged activated partial thromboplastin time	22	1.8	20	0.9
Hematology				
Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

*Per CTCAE version 4.0

[†]Elevated blood insulin was also observed in both regimens

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Brigatinib Plasma Concentrations

Strong CYP3A Inhibitors

Coadministration of itraconazole, a strong CYP3A inhibitor, increased brigatinib plasma concentrations and may result in increased adverse reactions [see *Clinical Pharmacology* (12.3)]. Avoid the concomitant use of strong CYP3A inhibitors with ALUNBRIG, including but not limited to certain antivirals (e.g., boceprevir, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin), antifungals (e.g., itraconazole, ketoconazole, posaconazole, voriconazole), and conivaptan. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib [see *Clinical Pharmacology* (12.3)]. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG by approximately 50% [see *Dosage and Administration* (2.3)].

7.2 Drugs That May Decrease Brigatinib Plasma Concentrations

Strong CYP3A Inducers

Coadministration of ALUNBRIG with rifampin, a strong CYP3A inducer, decreased brigatinib plasma concentrations and may result in decreased efficacy [see *Clinical Pharmacology* (12.3)]. Avoid the concomitant use of strong CYP3A inducers with ALUNBRIG, including but not limited to rifampin, carbamazepine, phenytoin, and St. John's Wort [see *Clinical Pharmacology* (12.3)].

7.3 Drugs That May Have Their Plasma Concentrations Altered by Brigatinib

CYP3A Substrates

Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates. Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates [see *Use in Specific Populations* (8.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman [see *Data and Clinical Pharmacology* (12.1)]. There are no clinical data on the use of ALUNBRIG in pregnant women.

Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as

low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

ALUNBRIG can cause fetal harm [see *Use in Specific Populations (8.1)*].

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective [see *Drug Interaction (7.3)*].

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose [see *Nonclinical Toxicology (13.1)*].

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients.

8.6 Hepatic Impairment

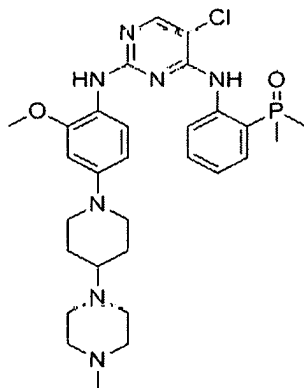
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST). The pharmacokinetics and safety of ALUNBRIG in patients with moderate or severe hepatic impairment have not been studied [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CL_{cr}) 30 to 89 mL/min estimated by Cockcroft-Gault]. The pharmacokinetics and safety of ALUNBRIG in patients with severe renal impairment (CL_{cr} 15 to 29 mL/min estimated by Cockcroft-Gault) have not been studied [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Brigatinib is a kinase inhibitor. The chemical name for brigatinib is 5-chloro-N¹-[2-(dimethylphosphoryl)phenyl]-N²-(2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl)pyrimidine-2,4-diamine. The molecular formula is C₂₉H₃₉ClN₇O₂P which corresponds to a formula weight of 584.10 g/mol. Brigatinib has no chiral centers. The chemical structure is shown below:



Brigatinib is an off-white to beige/tan solid. The pK_as were determined to be: 1.73 ± 0.02 (base), 3.65 ± 0.01 (base), 4.72 ± 0.01 (base), and 8.04 ± 0.01 (base).

ALUNBRIG is supplied for oral use as film-coated tablets containing 30 mg or 90 mg of brigatinib and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor with in vitro activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. Brigatinib also inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.

At clinically achievable concentrations (≤ 500 nM), brigatinib inhibited the in vitro viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited in vivo anti-tumor activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on crizotinib. Brigatinib also reduced tumor burden and prolonged survival in mice implanted intracranially with an ALK-driven tumor cell line.

12.2 Pharmacodynamics

Brigatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

Cardiac Electrophysiology

The QT interval prolongation potential of ALUNBRIG was assessed in 123 patients following once daily ALUNBRIG doses of 30 mg (1/6th of the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose). ALUNBRIG did not prolong the QT interval to a clinically relevant extent.

12.3 Pharmacokinetics

The geometric mean (CV%) steady-state maximum concentration (C_{max}) of brigatinib at ALUNBRIG doses of 90 mg and 180 mg once daily was 552 (65%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding area under the concentration-time curve (AUC_{0-Tau}) was 8165 (57%) ng·h/mL and 20276 (56%) ng·h/mL. After a single dose and repeat dosing of ALUNBRIG, systemic

exposure of brigatinib was dose proportional over the dose range of 60 mg (0.3 times the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose) once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Absorption

Following administration of single oral doses of ALUNBRIG of 30 to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours.

Effect of Food

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) compared to the C_{max} and AUC after overnight fasting.

Distribution

Brigatinib is 66% bound to human plasma proteins and the binding is not concentration-dependent in vitro. The blood-to-plasma concentration ratio is 0.69. Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent volume of distribution (V_z/F) of brigatinib at steady-state was 153 L.

Elimination

Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent oral clearance (CL/F) of brigatinib at steady-state is 12.7 L/h and the mean plasma elimination half-life is 25 hours.

Metabolism

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 in vitro. Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic pathways. Unchanged brigatinib (92%) and its primary metabolite, AP26123 (3.5%), were the major circulating radioactive components. The steady-state AUC of AP26123 was less than 10% of AUC of brigatinib exposure in patients. The metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib in vitro.

Excretion

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, 65% of the administered dose was recovered in feces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively.

Specific Populations

Age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of brigatinib.

Hepatic Impairment

As hepatic elimination is a major route of excretion for brigatinib, hepatic impairment may result in increased plasma brigatinib concentrations. Based on a population pharmacokinetic analysis, brigatinib exposures were similar between 49 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST) and 377 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of brigatinib in patients with moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) to severe (total bilirubin greater than 3.0 times ULN and any AST) hepatic impairment has not been studied.

Renal Impairment

Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment (CL_{cr} 60 to less than 90 mL/min), 34 subjects with moderate renal impairment (CL_{cr} 30 to less than 60 mL/min) and 270 subjects with normal renal function (CL_{cr} greater than or equal to 90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (CL_{cr} less than 30 mL/min) were not included in clinical trials.

Drug Interactions

Effects of Other Drugs on Brigatinib

Strong CYP3A Inhibitors: Coadministration of 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg dose of ALUNBRIG increased brigatinib C_{max} by 21% and AUC_{0-INF} by 101%, relative to a 90 mg dose of ALUNBRIG administered alone [see *Dosage and Administration* (2.3) and *Drug Interactions* (7.1)].

Strong CYP2C8 Inhibitors: Coadministration of 600 mg twice daily doses of gemfibrozil (a strong CYP2C8 inhibitor) with a single 90 mg dose of ALUNBRIG decreased brigatinib C_{max} by 41% and AUC_{0-INF} by 12%, relative to a 90 mg dose of ALUNBRIG administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown.

Strong CYP3A Inducers: Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 180 mg dose of ALUNBRIG decreased brigatinib C_{max} by 60% and AUC_{0-12h} by 80%, relative to a 180 mg dose of ALUNBRIG administered alone [see *Drug Interactions (7.2)*].

P-gp and BCRP Inhibitors: In vitro studies suggest that brigatinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given that brigatinib exhibits high solubility and high permeability in vitro, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib.

Other Transporters: Brigatinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump (BSEP).

Effects of Brigatinib on Other Drugs

Transporter Substrates: Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K in vitro. Therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters. Brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or BSEP.

CYP Substrates: Brigatinib and its primary metabolite, AP26123, did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations.

Brigatinib, at clinically relevant plasma concentrations, induced CYP3A via activation of the pregnane X receptor (PXR). Brigatinib may also induce CYP2C enzymes via the same mechanism at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with brigatinib.

Treatment with brigatinib resulted in chromosomal damage in an in vivo mammalian erythrocyte micronucleus in the rat, but was not mutagenic in the Ames or in vitro mammalian chromosome aberration tests.

Dedicated animal fertility studies were not conducted with brigatinib. Testicular toxicity was observed in repeat-dose animal studies at doses resulting in exposure as low as 0.2 times the exposure in patients at the 180 mg dose. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the 2-month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period.

14 CLINICAL STUDIES

The efficacy of ALUNBRIG was demonstrated in a two-arm, open-label, multicenter trial (ALTA, NCT02094573) in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib. The study required patients to have a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis[®] ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. Key eligibility criteria included an ECOG Performance Status of 0-2 and progression on crizotinib. Neurologically stable patients with central nervous system (CNS) metastases were permitted to enroll. Patients with a history of interstitial lung disease or drug-related pneumonitis or who had received crizotinib within 3 days of the first dose of brigatinib were excluded. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

A total of 222 patients were randomized to receive ALUNBRIG either 90 mg once daily (90 mg arm; n=112) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (90→180 mg arm; n=110). Randomization was stratified by brain metastases (present versus absent) and best prior response to crizotinib (complete or partial response versus any other response/unevaluable).

Baseline demographic characteristics of the overall study population were: median age 54 years (range 18 to 82, 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, and 95% never or former smokers. The disease characteristics of the overall study population were: Stage IV disease in 98%, adenocarcinoma histology in 97%, prior systemic chemotherapy in 74%, metastatic disease to the brain in 69% (61% had received prior radiation to the brain), bone metastases in 39%, and liver metastases in 26% of patients. Sixty-four percent of patients had an objective response to prior crizotinib.

The median duration of follow-up was 8 months (range: 0.1-20.2). Efficacy results from ALTA are summarized in Table 5.

Table 5: ALTA Efficacy Results

Efficacy parameter	IRC Assessment		Investigator Assessment	
	90 mg once daily (N=112)	90→180 mg once daily (N=110)	90 mg once daily (N=112)	90→180 mg once daily (N=110)
Overall Response Rate (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
Complete Response, n (%)	4 (3.6%)	5 (4.5%)	1 (0.9%)	4 (3.6%)
Partial Response, n (%)	50 (45%)	53 (48%)	49 (44%)	55 (50%)
Duration of Response, median in months (95% CI)	13.8 (7.4-NE)	13.8 (9.3-NE)	13.8 (5.6-13.8)	11.1 (9.2-13.8)

CI = Confidence Interval; NE = Not Estimable

IRC assessment of intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 44 patients with measurable brain metastases (≥ 10 mm in longest diameter) at baseline are summarized in Table 6. Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth $\geq 20\%$ from nadir, or unequivocal progression of intracranial non-target lesions) or death.

Table 6: Intracranial Objective Response in Patients with Measurable Brain Metastases in ALTA

Efficacy parameter	IRC Assessment	
	90 mg once daily (N=26)	90→180 mg once daily (N=18)
Intracranial Overall Response Rate, (95 % CI)	42% (23-63)	67% (41-87)
Complete Response, n (%)	2 (7.7%)	0
Partial Response, n (%)	9 (35%)	12 (67%)
Duration of Intracranial Response, median (months) (range)	NE (1.9+ - 9.2+)	5.6 (1.9+ - 9.2+)

CI = Confidence Interval; NE = Not Estimable

Among the 23 patients who exhibited an intracranial response, 78% of patients in the 90 mg arm and 68% of patients in the 90→180 mg arm maintained a response for at least 4 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

30 mg tablets: round, white to off-white film-coated tablet with “U3” debossed on one side and plain on the other side; available in:

Bottles of 21 tablets	NDC 76189-113-21
Bottles of 180 tablets	NDC 76189-113-18

90 mg tablets: oval, white to off-white film-coated tablet with “U7” debossed on one side and plain on the other side; available in:

Bottles of 7 tablets	NDC 76189-119-07
Bottles of 30 tablets	NDC 76189-119-30

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) (see USP).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms [see *Warnings and Precautions* (5.1)].

Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension [see *Warnings and Precautions* (5.2)].

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications [see *Warnings and Precautions* (5.3)].

Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms [see *Warnings and Precautions* (5.4)].

Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatinine phosphokinase (CPK) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms of unexplained muscle pain, tenderness, or weakness [see *Warnings and Precautions* (5.5)].

Pancreatic Enzyme Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment [see *Warnings and Precautions* (5.6)].

Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that anti-hyperglycemic medications may need to be adjusted during treatment with ALUNBRIG [see *Warnings and Precautions* (5.7)].

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity

Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm [see *Warnings and Precautions* (5.8) and *Use in Specific Populations* (8.1)].

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose [see *Use in Specific Populations* (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose [see *Use in Specific Populations* (8.3)].

Lactation

Advise females not to breastfeed during treatment with ALUNBRIG and for at least 1 week following the final dose [see *Use in Specific Populations* (8.2)].

Infertility

Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG [see *Use in Specific Populations* (8.3) and *Nonclinical Toxicology* (13.1)].

Drug Interactions

Advise patients to inform their health care provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG [see *Drug Interactions* (7)].

Dosing and Administration

Instruct patients to start with 90 mg of ALUNBRIG once daily for the first 7 days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food [see *Dosage and Administration (2.1)*].

Missed Dose

Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time [see *Dosage and Administration (2.1)*].

Manufactured for:

ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Cambridge, MA

PATIENT INFORMATION
ALUNBRIG (uh-lun-brig)
(brigatinib)
tablets

What is the most important information I should know about ALUNBRIG?

ALUNBRIG can cause serious side effects, including:

- **Lung problems. ALUNBRIG may cause severe or life-threatening swelling (inflammation) of the lungs any time during treatment, and can lead to death.** These lung problems happen **especially within the first week of treatment** with ALUNBRIG. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
 - trouble breathing or shortness of breath
 - cough with or without mucous
 - chest pain
 - fever
- **High blood pressure (hypertension).** ALUNBRIG may cause high blood pressure. Your healthcare provider will check your blood pressure before starting and during treatment with ALUNBRIG. Tell your healthcare provider right away if you get headaches, dizziness, blurred vision, chest pain or shortness of breath.
- **Slow heart rate (bradycardia).** ALUNBRIG may cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate during treatment with ALUNBRIG. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint during treatment with ALUNBRIG. Tell your healthcare provider if you start to take or have any changes in heart or blood pressure medicines.
- **Vision problems.** ALUNBRIG may cause vision problems. Your healthcare provider may stop ALUNBRIG and refer you to an eye specialist if you develop severe vision problems during treatment with ALUNBRIG. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
 - double vision
 - light hurting your eyes
 - seeing flashes of light
 - new or increased floaters
 - blurry vision
- **Muscle pain, tenderness, and weakness (myalgia).** ALUNBRIG may increase the level of an enzyme in your blood called creatine phosphokinase (CPK), which may be a sign of muscle damage. Your healthcare provider will do blood tests to check your blood levels of CPK during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Inflammation of the pancreas (pancreatitis).** ALUNBRIG may increase enzymes in your blood called amylase and lipase, which may be a sign of pancreatitis. Your healthcare provider will do blood tests to check your pancreatic enzyme blood levels during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of pancreatitis, including upper abdominal pain that may spread to the back and get worse with eating, weight loss, or nausea.
- **High blood sugar (hyperglycemia).** ALUNBRIG may increase your blood sugar levels. Your healthcare provider will do blood tests to check your blood sugar levels before starting and during treatment with ALUNBRIG. Your healthcare provider may need to start or change your blood sugar medicine to control your blood sugar levels. Tell your healthcare provider right away if you get new or worsening signs and symptoms of hyperglycemia, including:
 - feeling very thirsty
 - feeling sick to your stomach
 - needing to urinate more than usual
 - feeling weak or tired
 - feeling very hungry
 - feeling confused

See “What are the possible side effects of ALUNBRIG?” for information about side effects.

What is ALUNBRIG?

ALUNBRIG is a prescription medicine used to treat people with non-small cell lung cancer (NSCLC):

- that has a certain type of abnormal anaplastic lymphoma kinase (ALK) gene, **and**
- that has spread to other parts of your body, **and**
- who have taken the medicine crizotinib, but their NSCLC worsened or they cannot tolerate taking crizotinib.

It is not known if ALUNBRIG is safe and effective in children.

Before you take ALUNBRIG, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems
- have high blood pressure
- have a slow heartbeat
- have any vision problems
- have or have had pancreatitis
- have diabetes mellitus or glucose intolerance
- are pregnant or plan to become pregnant. ALUNBRIG can harm your unborn baby. Tell your healthcare provider right

away if you become pregnant during treatment with ALUNBRIG or think you may be pregnant.

- o **Females** who are able to become pregnant should use effective non-hormonal birth control during treatment with ALUNBRIG and for at least 4 months after the final dose of ALUNBRIG. Birth control pills (oral contraceptives) and other hormonal forms of birth control may not be effective if used during treatment with ALUNBRIG. Talk to your healthcare provider about birth control choices that are right for you during treatment with ALUNBRIG.
- o **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with ALUNBRIG and for at least 3 months after the final dose of ALUNBRIG.
- are breastfeeding or plan to breastfeed. It is not known if ALUNBRIG passes into your breast milk. Do not breastfeed during treatment with ALUNBRIG and for 1 week after the final dose of ALUNBRIG.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

How should I take ALUNBRIG?

- Take ALUNBRIG exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ALUNBRIG unless your healthcare provider tells you to.
- Your healthcare provider will start you on a low dose (90 mg) of ALUNBRIG for the first 7 days of treatment. If you tolerate this dose of ALUNBRIG well, your healthcare provider may increase your dose after the first 7 days of treatment.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ALUNBRIG if you have side effects.
- Take ALUNBRIG 1 time each day.
- Take ALUNBRIG with or without food.
- Swallow ALUNBRIG tablets whole. Do not crush or chew tablets.
- If you miss a dose of ALUNBRIG, do not take the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of ALUNBRIG, do not take an extra dose. Take your next dose at your regular time.

What should I avoid while taking ALUNBRIG?

- Avoid eating grapefruit or drinking grapefruit juice during treatment with ALUNBRIG. Grapefruit may increase the amount of ALUNBRIG in your blood.

What are the possible side effects of ALUNBRIG?

ALUNBRIG may cause serious side effects, including:

- See "What is the most important information I should know about ALUNBRIG?"

The most common side effects of ALUNBRIG include:

• nausea	• fatigue	• headache
• diarrhea	• cough	

ALUNBRIG may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of ALUNBRIG. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ALUNBRIG?

- Store ALUNBRIG at room temperature 20°C to 25°C (68°F to 77°F).

Keep ALUNBRIG and all medicines out of the reach of children.

General information about the safe and effective use of ALUNBRIG.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information. Do not use ALUNBRIG for a condition for which it was not prescribed. Do not give ALUNBRIG to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ALUNBRIG that is written for health professionals.

What are the ingredients in ALUNBRIG?

Active ingredient: brigatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

Manufactured for: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA
For more information, go to www.alunbrig.com or call 1-844-217-6468.

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: April 2017

Store at controlled room temperature 58° to 77°F (20° to 25°C); excursions permitted between 58° to 86°F (15°C to 30°C) (see USP) **Usual Dose:** See prescribing information.

KEEP AWAY FROM CHILDREN

LA00333A

NDC 20189-113-21

Alunbrig[™]
(brigatinib) tablets

30 mg Rx Only

Each tablet contains 30 mg brigatinib

21 Tablets

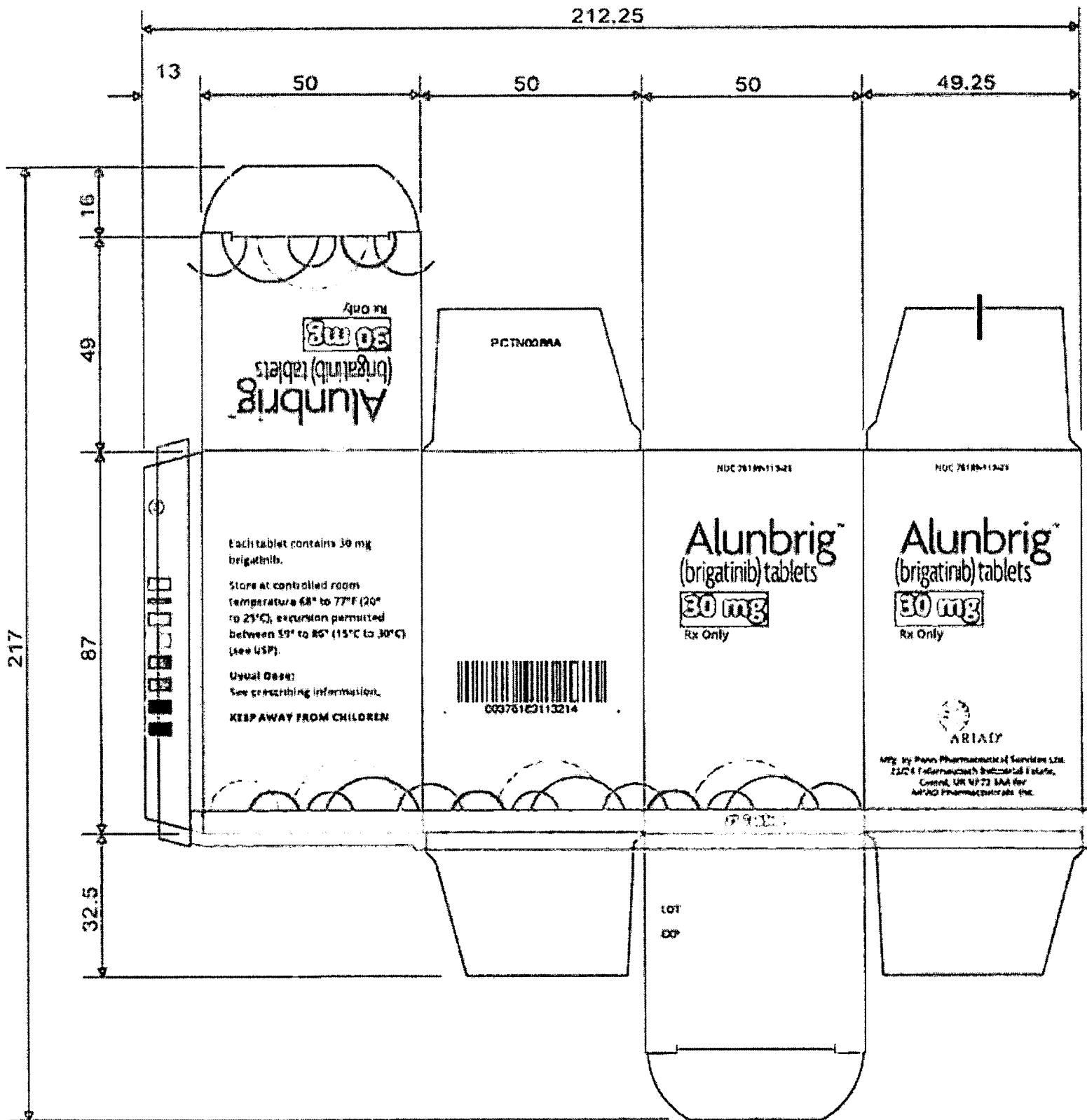
ARIAD

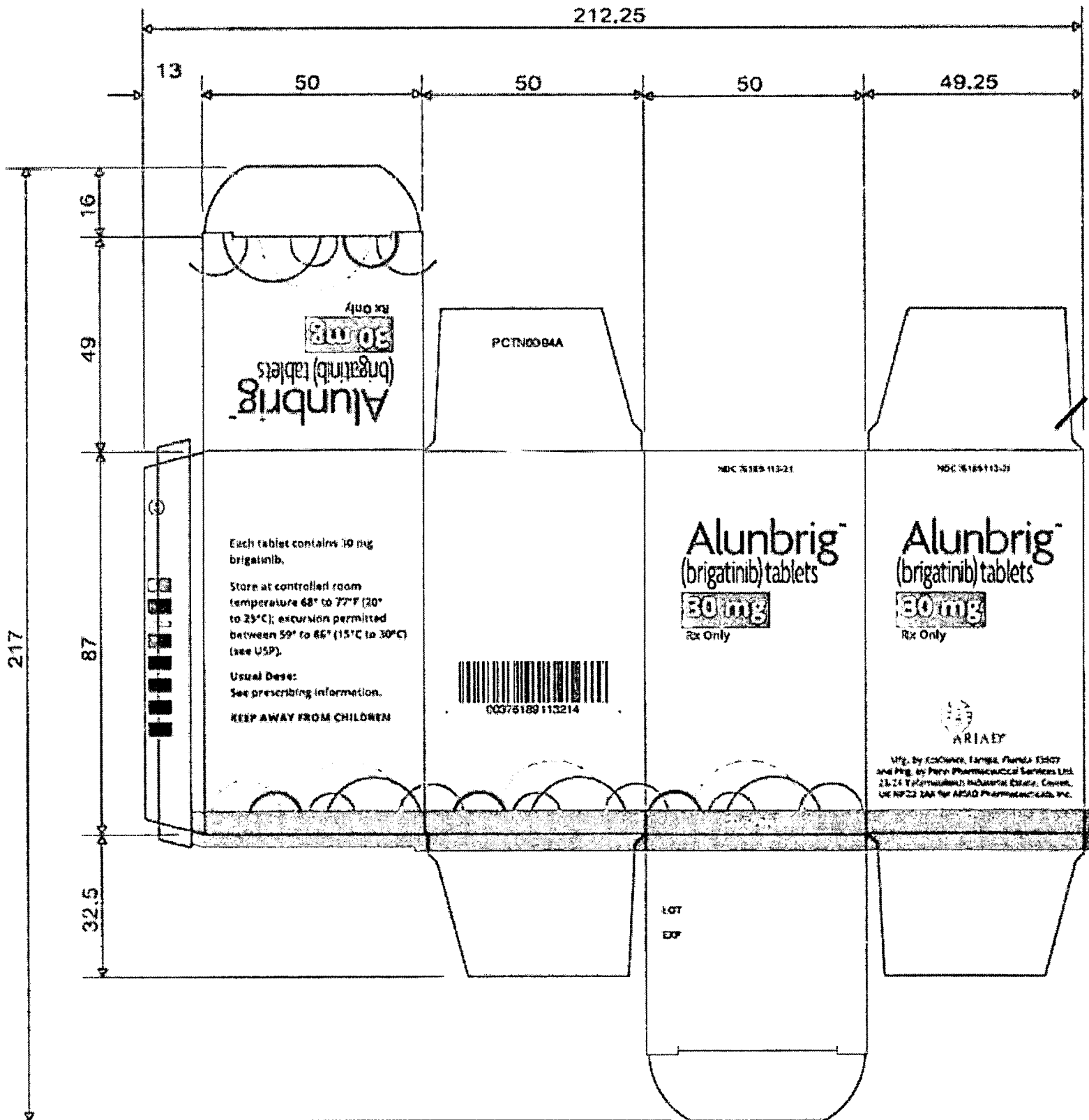
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Mfg. by Perrin Pharmaceuticals, Inc. (Perrin)
 20247 McArthur Rd., Suite 100
 Green, TX 75223-1447
 ARIAD Pharmaceuticals, Inc.

Measure bar should be 150mm at 100% scale





Store at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) (See USP Controlled Room Temperature). See prescribing information.

KEEP AWAY FROM CHILDREN

LA00311A

Lot:
 Exp:
 180 Tablets

NDC 76189-113-18

Alunbrig[™]

(brigatinib) tablets

30 mg

Rx Only

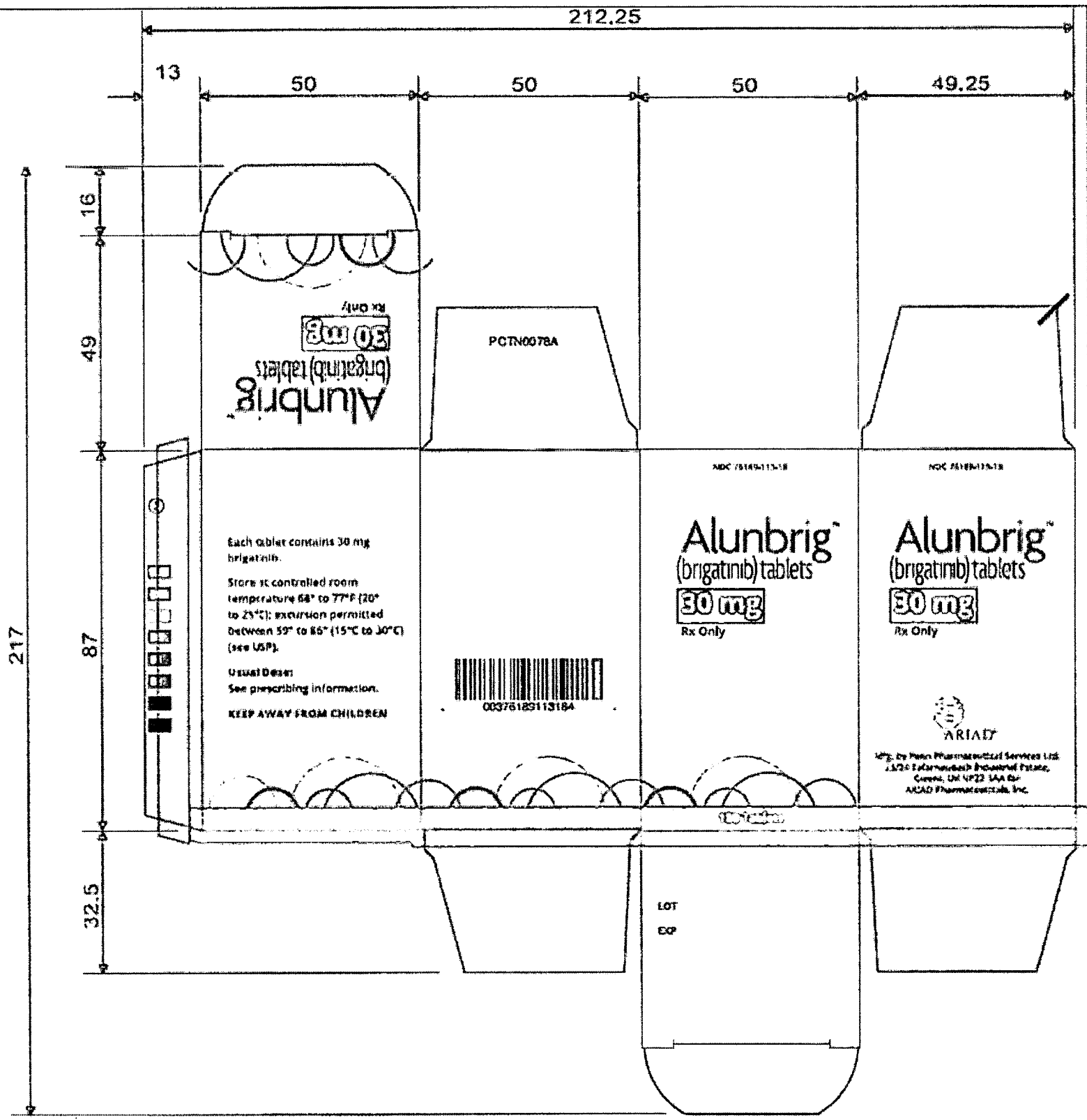
Each tablet contains 30 mg brigatinib



ARIAD

Mfg. by Pharm. Pharmatech (USA) Inc. (PPI), a subsidiary of Pharm. Pharmatech (USA) Inc. (PPI), 10000 N. 10th Ave., Suite 100, Phoenix, AZ 85021-1000. © 2018 PPI. All rights reserved.

Measure bar should be 150mm at 100% scale



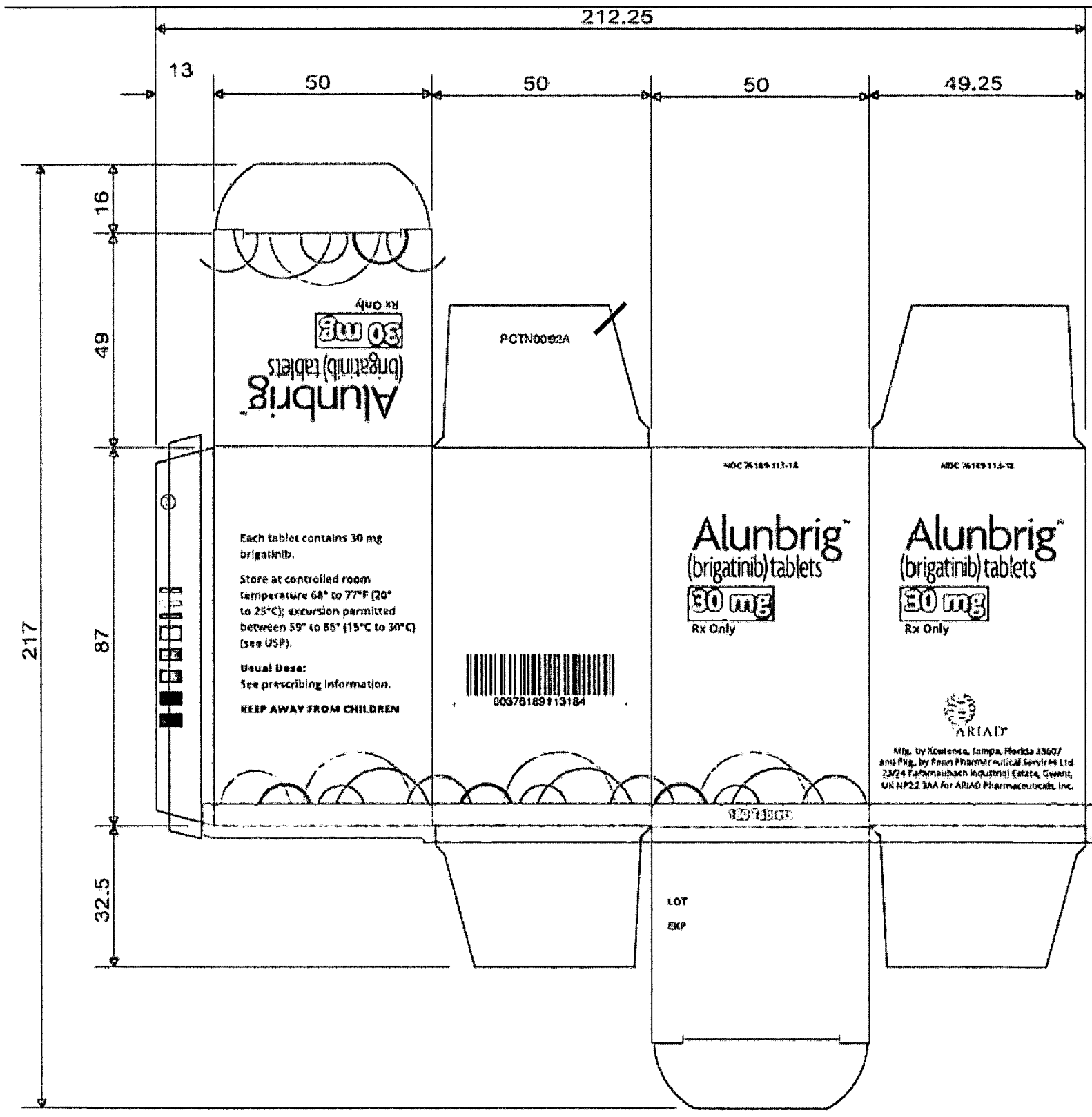
003769060000

Store at controlled room temperature 68° to 77°F (20° to 25°C); excursions permitted between 59° to 86°F (15°C to 30°C) (see USP).
Usual Dose:
See prescription information.
KEEP AWAY FROM CHILDREN
L400380A

NDC 74189-113-18
Alunbrig[™]
(brigatinib) tablets
30 mg TABLETS **Rx Only**
Each tablet contains 30 mg brigatinib
180 Tablets
AXIAT

Mfg. by Xcelience, Tampa, Florida 33607
Whl Pkg. by Perini Pharmaceutical Services Ltd.
2324 Trafalgar Industrial Estate, Coventry, UK N12 3AA for Alunbrig Pharmaceuticals Inc.

Measure bar should be 150mm at 100% scale





00376189719070

Store at controlled
room temperature
68° to 77° (20° to 25°C);
excursion permitted
between 59° to 86°F
(15°C to 30°C) (see USP).

Usual Dose:
See prescribing
information.

KEEP AWAY
FROM CHILDREN

LAO341A

00376189719070

Alunbrig[®]
(brigatinib) tablets

90 mg Rx Only

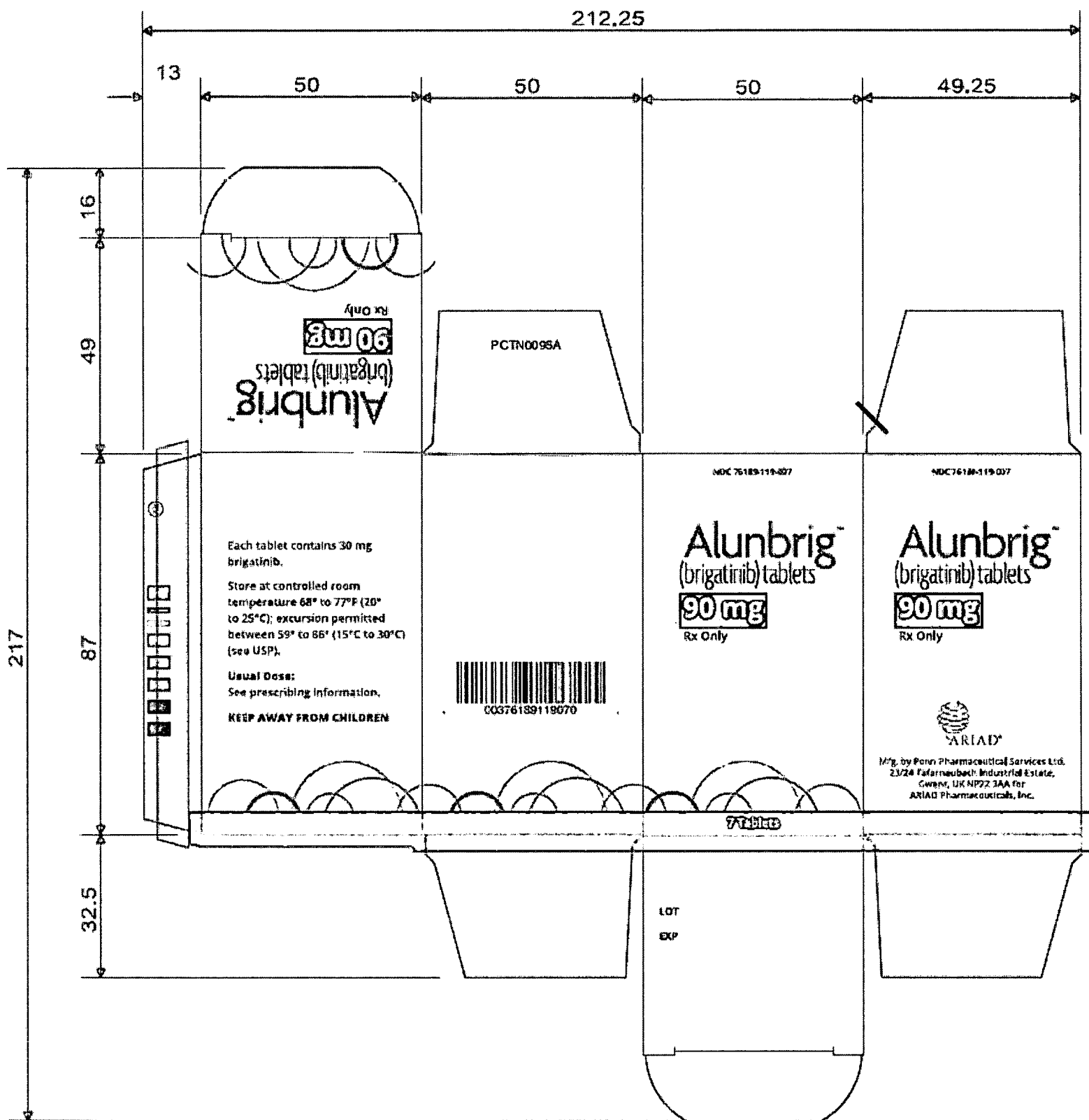
Each tablet contains 90 mg brigatinib

7 Tablets

ARIAT

Mfg. by Parn Pharmaceutical Services Ltd.
Zurich, Switzerland
Glenview, IL 60045, USA
ARIAT Pharmaceuticals, Inc.

Measure bar should be 150mm at 100% scale



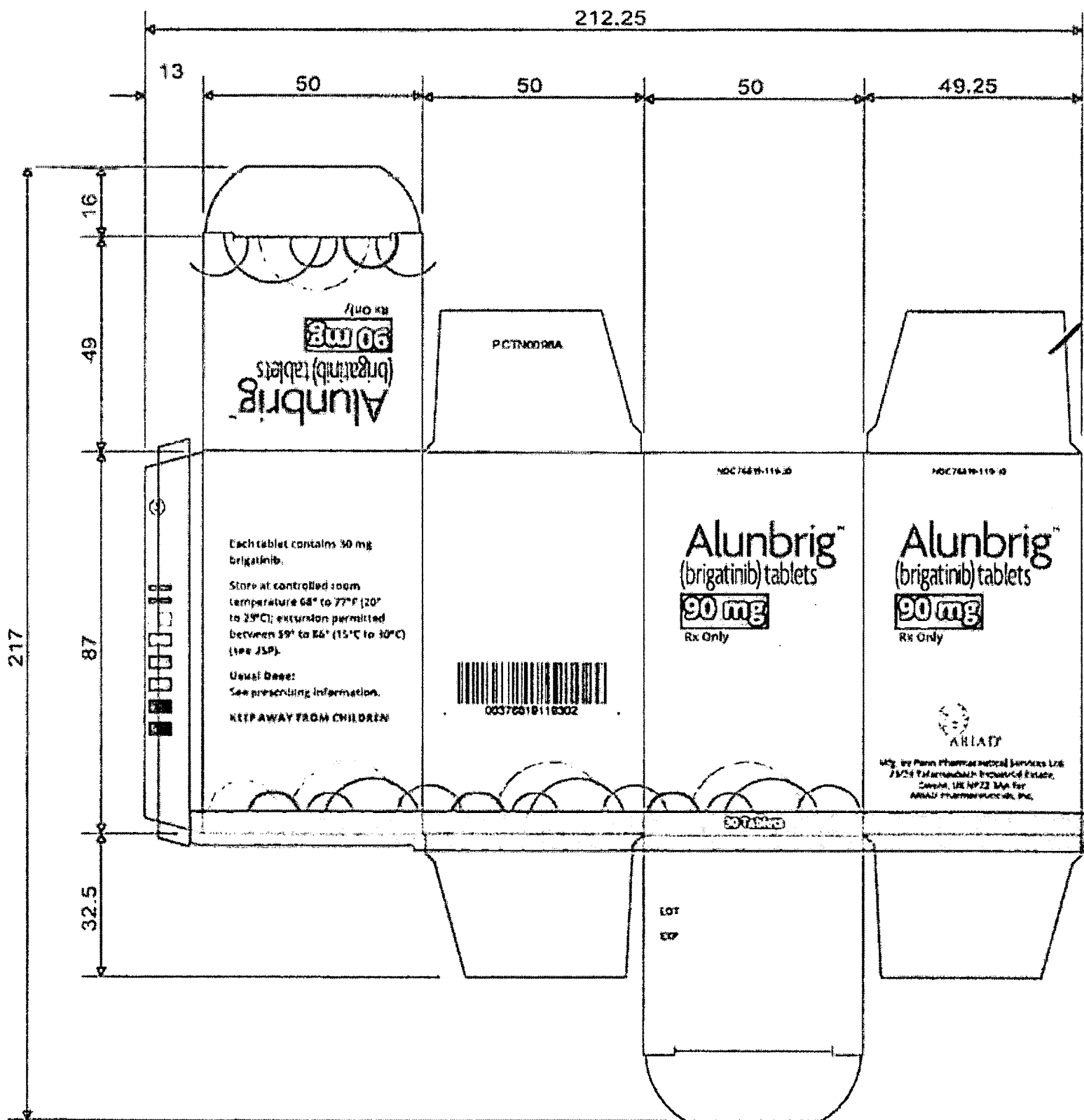


EXHIBIT D

12/736,910 PHOSPHORUS DERIVATIVES AS KINASE INHIBITORS 13396-020-999 06-16-2017::10:20:37

Patent Term Adjustments

Patent Term Adjustment (PTA) for Application Number: 12/736,910

Filing or 371(c) Date:	01-17-2012	Overlapping Days Between {A and B} or {A and C}:	0
Issue Date of Patent:	04-21-2015	Non-Overlapping USPTO Delays:	887
A Delays:	439	PTO Manual Adjustments:	-126
B Delays:	448	Applicant Delays:	135
C Delays:	0	Total PTA Adjustments:	626

Patent Term Adjustment History

Explanation Of Calculations

Number	Date	Contents Description	PTO (Days)	APPL (Days)	Start
158	02-17-2017	Adjustment of PTA Calculation by PTO	190		0
150	02-19-2016	Adjustment of PTA Calculation by PTO		190	0
149	02-19-2016	Adjustment of PTA Calculation by PTO		126	0
145.5	04-21-2015	PTA 36 Months	448		145.4
145.4	11-22-2010	Commencement Date			0
145	04-21-2015	Patent Issue Date Used in PTA Calculation			0
144	03-11-2015	Export to Final Data Capture			0
143	03-10-2015	Dispatch to FDC			0
142	03-10-2015	Dispatch to FDC			0
141	03-06-2015	Finished Initial Data Capture			0
140	03-09-2015	Mail Response to 312 Amendment (PTO-271)		15	132
139	03-06-2015	Office Action Review			0
138	03-06-2015	Office Action Review			0
137	03-06-2015	Office Action Review			0
136	03-06-2015	Reasons for Allowance			0
135	03-06-2015	Examiner's Amendment Communication			0
134	03-06-2015	Response to Amendment under Rule 312			0
133	02-28-2015	Pubs Case Remand to TC			0

132	02-23-2015	Amendment after Notice of Allowance (Rule 312)	0
131	01-15-2015	Response to Reasons for Allowance	0
130	02-27-2015	Application Is Considered Ready for Issue	0
129	02-23-2015	Issue Fee Payment Verified	0
128	02-23-2015	Issue Fee Payment Received	0
127	01-27-2015	Printer Rush- No mailing	0
126	01-27-2015	Mailing Corrected Notice of Allowability	0
125	01-24-2015	Office Action Review	0
124	01-24-2015	Office Action Review	0
123	01-24-2015	Office Action Review	0
122	01-24-2015	Office Action Review	0
121	01-22-2015	Interview Summary - Examiner Initiated - Telephonic	0
120	01-22-2015	Interview Summary - Examiner Initiated	0
119	01-23-2015	Examiner's Amendment Communication	0
118	01-23-2015	Corrected Notice of Allowability	0
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115	01-20-2015	Mailing Corrected Notice of Allowability	0
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113	01-16-2015	Office Action Review	0
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105	11-21-2014	Office Action Review		0
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103	11-21-2014	Office Action Review		0
102	11-21-2014	Issue Revision Completed		0
101	11-21-2014	Document Verification		0
100	11-21-2014	Notice of Allowance Data Verification Completed		0
99	11-21-2014	Case Docketed to Examiner in GAU		0
98	11-18-2014	Add FAOM 1.25 Count		0
97	11-18-2014	Subtract FAOM 1.00 Count		0
96	10-30-2014	Interview Summary - Applicant Initiated - Conference		0
95	10-30-2014	Interview Summary- Applicant Initiated		0
94	11-18-2014	Reasons for Allowance		0
93	11-18-2014	Examiner's Amendment Communication		0
92	11-18-2014	Allowability Notice		0
91	10-14-2014	Information Disclosure Statement considered		0
90	09-19-2014	Reference capture on IDS		0
89	09-19-2014	Information Disclosure Statement (IDS) Filed		0
86	10-02-2014	Date Forwarded to Examiner		0
85	09-19-2014	Amendment Submitted/Entered with Filing of CPA/RCE		0
84	09-19-2014	Request for Continued Examination (RCE)	88	74
83	10-02-2014	Disposal for a RCE / CPA / R129		0
82	09-19-2014	Request for Extension of Time - Granted		0
81	09-26-	Change in Power of Attorney (May Include Associate		0

	2014	POA)		
80	09-24-2014	Correspondence Address Change		0
79	09-19-2014	Information Disclosure Statement (IDS) Filed		0
78	09-19-2014	Workflow - Request for RCE - Begin		0
76	03-23-2014	Electronic Review		0
75	03-21-2014	Email Notification		0
74	03-21-2014	Mail Final Rejection (PTOL - 326)		0
73	03-18-2014	Office Action Review		0
72	03-17-2014	Final Rejection		0
71	03-14-2014	Information Disclosure Statement considered		0
70	01-21-2014	Reference capture on IDS		0
69	01-21-2014	Information Disclosure Statement (IDS) Filed		0
68	02-03-2014	Date Forwarded to Examiner		0
67	01-21-2014	Response after Non-Final Action	32	62
66	01-21-2014	Request for Extension of Time - Granted		0
65	01-21-2014	Information Disclosure Statement (IDS) Filed		0
64	09-20-2013	Electronic Review		0
63	09-20-2013	Email Notification		0
62	09-20-2013	Mail Non-Final Rejection		0
61	09-18-2013	Office Action Review		0
60	09-17-2013	Non-Final Rejection		0
57	07-01-2013	Information Disclosure Statement considered		0
54	09-10-2012	Information Disclosure Statement considered		0
53	07-15-2011	Information Disclosure Statement considered		0
42	07-01-2013	Information Disclosure Statement (IDS) Filed		0

41	07-01-2013	Reference capture on IDS		0
40	07-01-2013	Information Disclosure Statement (IDS) Filed		0
39	07-04-2013	Date Forwarded to Examiner		0
38	07-01-2013	Response to Election / Restriction Filed		0
37	07-01-2013	Request for Extension of Time - Granted		0
36	07-01-2013	Information Disclosure Statement (IDS) Filed		0
35	04-07-2013	Electronic Review		0
34	04-05-2013	Email Notification		0
33	04-05-2013	Mail Restriction Requirement	439	145.4
32	04-02-2013	Office Action Review		0
31	03-28-2013	Restriction/Election Requirement		0
29	09-10-2012	Reference capture on IDS		0
28	04-27-2012	Corrected filing receipt		0
27	09-10-2012	Information Disclosure Statement (IDS) Filed		0
26	09-10-2012	Information Disclosure Statement (IDS) Filed		0
25	08-10-2012	Email Notification		0
24	08-09-2012	PG-Pub Issue Notification		0
23	07-14-2012	Case Docketed to Examiner in GAU		0
22	07-15-2011	Reference capture on IDS		0
21	07-15-2011	Information Disclosure Statement (IDS) Filed		0
20	11-22-2010	Request for Foreign Priority (Priority Papers May Be Included)		0
19	11-22-2010	Preliminary Amendment		0
18	05-16-2012	Application Dispatched from OIPE		0
17	05-01-2012	Filing Receipt - Corrected		0
16	01-17-2012	371 Completion Date		0

15	04-20-2012	Sent to Classification Contractor	0
14	04-20-2012	Filing Receipt	0
13	04-20-2012	Notice of DO/EO Acceptance Mailed	0
12	01-17-2012	Additional Application Filing Fees	0
11	01-17-2012	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applicant	0
10	04-12-2012	Mail-Petition Decision - Granted	0
9	04-12-2012	Petition Decision - Granted	0
8	01-17-2012	Petition Entered	0
7	09-13-2011	Mail-Petition Decision - Dismissed	0
6	09-13-2011	Petition Decision - Dismissed	0
5	07-15-2011	Information Disclosure Statement (IDS) Filed	0
4	07-11-2011	Petition Entered	0
3	12-06-2010	Notice of DO/EO Missing Requirements Mailed	0
2	11-30-2010	Cleared by OIPE CSR	0
1	11-22-2010	Initial Exam Team nn	0
0.5	05-21-2009	International Filing date	0

Close Window

EXHIBIT E



US009012462B2

(12) **United States Patent**
Wang et al.

(10) **Patent No.:** **US 9,012,462 B2**
(45) **Date of Patent:** **Apr. 21, 2015**

(54) **PHOSPHOROUS DERIVATIVES AS KINASE INHIBITORS**

(75) Inventors: **Yihan Wang**, Newton, MA (US); **Wei-Sheng Huang**, Acton, MA (US); **Shuangying Liu**, Wellesley, MA (US); **William C. Shakespeare**, Southborough, MA (US); **R. Mathew Thomas**, Sharon, MA (US); **Jiwei Qi**, West Roxbury, MA (US); **Feng Li**, Winchester, MA (US); **Xiaotian Zhu**, Newton, MA (US); **Anna Kohlman**, Winchester, MA (US); **David C. Dalgarno**, Brookline, MA (US); **Jan Antoinette C. Romero**, Somerville, MA (US); **Dong Zou**, Concord, MA (US)

(73) Assignee: **Ariad Pharmaceuticals, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 752 days.

(21) Appl. No.: **12/736,910**

(22) PCT Filed: **May 21, 2009**
(Under 37 CFR 1.47)

(86) PCT No.: **PCT/US2009/044918**
§ 371 (c)(1),
(2), (4) Date: **Jan. 17, 2012**

(87) PCT Pub. No.: **WO2009/143389**
PCT Pub. Date: **Nov. 26, 2009**

(65) **Prior Publication Data**
US 2012/0202776 A1 Aug. 9, 2012

Related U.S. Application Data

(60) Provisional application No. 61/128,317, filed on May 21, 2008, provisional application No. 61/137,490, filed on Jul. 31, 2008, provisional application No. 61/188,796, filed on Aug. 13, 2008, provisional application No. 61/192,938, filed on Sep. 23, 2008, provisional application No. 61/192,964, filed on Sep. 23, 2008.

(51) Int. Cl.
A61K 31/506 (2006.01)
C07F 9/30 (2006.01)
C07D 239/48 (2006.01)
C07F 9/6509 (2006.01)
C07F 9/6512 (2006.01)
C07F 9/6521 (2006.01)
C07F 9/6558 (2006.01)
C07F 9/6561 (2006.01)
C07F 9/6568 (2006.01)
C07F 9/6571 (2006.01)

(52) U.S. Cl.
CPC **C07D 239/48** (2013.01); **C07F 9/650941** (2013.01); **C07F 9/65122** (2013.01); **C07F**

9/65127 (2013.01); **C07F 9/65217** (2013.01); **C07F 9/65218** (2013.01); **C07F 9/65583** (2013.01); **C07F 9/65586** (2013.01); **C07F 9/6561** (2013.01); **C07F 9/65616** (2013.01); **C07F 9/65685** (2013.01); **C07F 9/657172** (2013.01)

(58) **Field of Classification Search**
USPC 514/258.1, 275; 544/243, 280, 323
See application file for complete search history.

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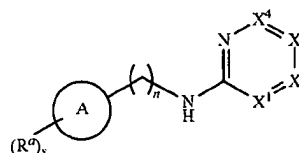
Primary Examiner — Rebecca Anderson

Assistant Examiner — Karen Cheng

(74) *Attorney, Agent, or Firm* — David L. Berstein

(57) ABSTRACT

The invention features compounds of the general formula (I) in which the variable groups are as defined herein, and to their preparation and use.



(I)

(56)

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PHOSPHOROUS DERIVATIVES AS KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims benefit under 35 U.S.C. §371 of International Application No. PCT/US2009/044918 (published PCT application No. WO 2009/143389), filed May 21, 2009, which claims priority to 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 61/128,317, filed May 21, 2008, U.S. Provisional Patent Application No. 61/137,490, filed Jul. 31, 2008, U.S. Provisional Patent Application No. 61/188,796, filed Aug. 13, 2008, U.S. Provisional Patent Application No. 61/192,938, filed Sep. 23, 2008 and U.S. Provisional Application No. 61/192,964, filed Sep. 23, 2008, the entire contents of each of the above-referenced applications are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The protein kinases represent a large family of proteins which play a central role in the regulation of a wide variety of cellular processes and maintain control over cellular function. A partial, non limiting, list of such kinases includes ALK, abl, Akt, bcr-abl, Blk, Brk, c-kit, c-met, c-src, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, bRaf, cRaf, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Pak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, flt-3, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak1, Jak2, Jak3, KDR, Lck, Lyn, FAK, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, Pim-1, Pl3k, TRK and Zap70. Abnormal protein kinase activity has been related to several disorders, ranging from non-life threatening diseases such as psoriasis to extremely serious diseases such as cancers.

In view of this large number of protein kinases and the multitude of protein kinase-related diseases, there is an ever-existing need to provide new classes of compounds with increased selectivity that are useful as protein kinase inhibitors and therefore useful in the treatment of protein tyrosine-kinase related diseases.

The invention concerns a new family of phosphorous compounds and their use in treating cancers and other diseases.

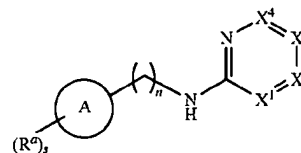
DESCRIPTION OF THE INVENTION

1. General Description of Compounds of the Invention

Compounds of the invention can have a broad range of useful biological and pharmacological activities, permitting their use in pharmaceutical compositions and methods for treating cancer (including lymphoma, solid tumors and leukemia among other cancers), including, also among others, advanced cases and cases which are resistant or refractory to one or more other treatments.

Included are compounds of Formula I, and tautomers and pharmaceutically acceptable salts and solvate thereof:

Formula I



wherein

X¹ is NR^{b1} or CR^b;

X² is NR^{c1} or CR^c;

X³ is NR^{d1} or CR^d;

X⁴ is NR^{e1} or CR^e;

Ring A is an aryl, a 5- or a 6-membered heteroaryl ring which contains 1 to 4 heteroatoms selected from N, O and S(O);

at each occurrence R^a, R^b, R^c, R^d and R^e are independently selected from the group consisting of halo, —CN, —NO₂, —R¹, —OR², —O—NR¹R², —NR¹R², —NR¹—NR¹R², —NR¹—OR², —C(O)YR², —OC(O)YR², —NR¹C(O)YR², —SC(O)YR², —NR¹C(=S)YR², —OC(=S)YR², —C(=S)YR², —YC(=NR¹)YR², —YC(=N—OR¹)YR², —YC(=N—NR¹R²)YR², —YP(=O)(YR³)(YR³), —Si(R^{3a})₃, —NR¹SO₂R², —S(O)₂R², —SO₂NR¹R² and —NR¹SO₂NR¹R², and R^{b1}, R^{c1}, R^{d1} and R^{e1} are absent;

wherein each Y is independently a bond, —O—, —S— or —NR¹—; or

alternatively two adjacent substituents selected from R^b, R^{b1}, R^c, R^{c1}, R^d, R^{d1}, R^e and R^{e1}; or two adjacent R^a moieties, can form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4 heteroatoms selected from N, O and S(O), and which is substituted with one to four R^f moieties wherein;

each R^f moiety is independently selected from the group consisting of halo, —O—, —S—, —CN, —NO₂, —R¹, —OR², —O—NR¹R², —NR¹R², —NR¹—NR¹R², —NR¹—OR², —C(O)YR², —OC(O)YR², —NR¹C(O)YR², —SC(O)YR², —NR¹C(=S)YR², —OC(=S)YR², —C(=S)YR², —YC(=NR¹)YR², —YC(=N—OR¹)YR², —YC(=N—NR¹R²)YR², —YP(=O)(YR³)(YR³), —Si(R^{3a})₃, —NR¹SO₂R², —S(O)₂R², —SO₂NR¹R² and —NR¹SO₂NR¹R²; or alternatively two adjacent R^f moieties can form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, optionally substituted; and which contains 0-4 heteroatoms selected from N, O and S(O); at least one of R^a, R^b, R^c, R^d, R^e, R^f, R^{b1}, R^{c1}, R^{d1} and R^{e1}, when present, is or contains —P(=O)(R³)₂ or a ring system containing the moiety —P(=O)(R³)— as a ring member.

r is 0, 1 or 2;

s is 1, 2, 3, 4 or 5

n is 0 or 1;

each occurrence of Y is independently a bond, —O—, —S— or —NR¹—;

each occurrence of R¹ and R² is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic and heteroaryl;

each occurrence of R³ is independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic and heteroaryl, or two adjacent R³ moieties combine to form a ring system including a phosphorous atom;

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each occurrence of R^{3a} is independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic, and heteroaryl;

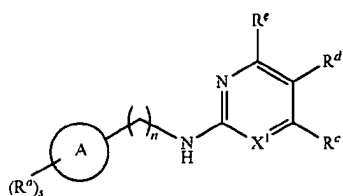
alternatively, each NR^1R^2 moiety may be a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which can be optionally substituted and which contains 0-2 additional heteroatoms selected from N, O and S(O)_n; and

each of the foregoing alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocyclic moiety is optionally substituted.

The foregoing definitions are further elaborated upon and exemplified below and apply to all subsequent occurrences except to the extent otherwise specified.

2. Featured Classes of Compounds and their Use, Generally

One class of compounds which is of special interest for use in the invention are compounds of Formula I, as described above in Part 1, in which X^2 is CR^c , X^3 is CR^d and X^4 is CR^e . This class is illustrated by compounds of Formula IA:



Formula IA

wherein

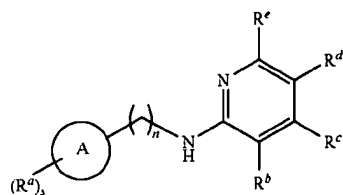
X^1 is N or CR^b ; and Ring A, R^a , R^b , R^c , R^d , R^e , n, and s are as defined in Formula I.

One class of interest includes compounds in which Ring A is a phenyl.

Another class of interest includes compounds in which Ring A is a 5- or 6-membered heteroaryl.

Another class of compounds which is of special interest for use in the invention are compounds of Formula Ia, as described above, in which X^1 is CR^b .

This class is illustrated by compounds of Formula IB:



Formula IB

A subclass of interest include compound of Formula IB in which n is 0.

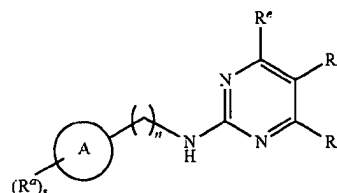
Another subclass of interest includes compounds of Formula IB in which n is 1.

Another subclass of interest includes compounds of Formula IB in which Ring A is phenyl.

Of special interest is another class of compounds of Formula IA as described above in Part 1 in which X^1 is N. This class is illustrated by compounds of Formula IC:

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Formula IC



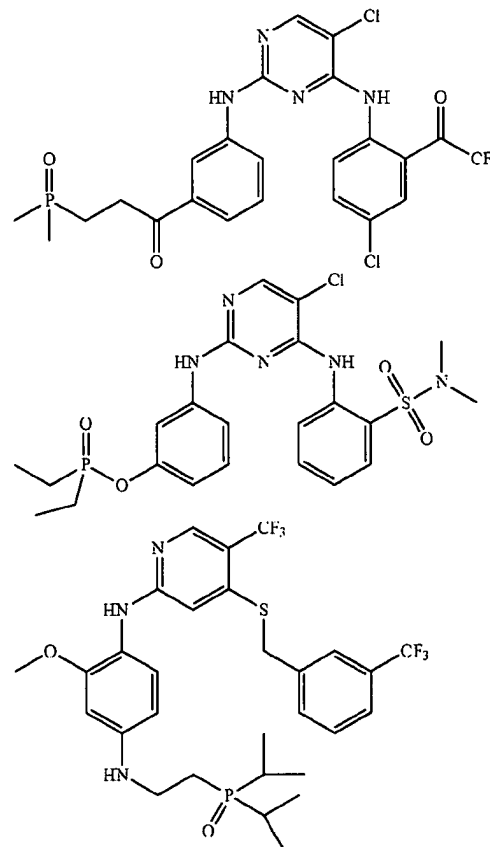
A subclass of interest include compound of Formula IC in which n is 0.

Another subclass of interest includes compounds of Formula IC in which n is 1.

Another subclass of interest includes compounds of Formula IC in which Ring A is phenyl.

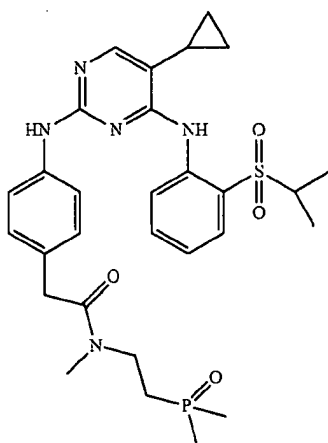
In Formulas IB and IC, s, R^a , R^b , R^c , R^d and R^e are as defined above in Formula I. In a particular embodiment of the previous classes and subclasses, one of R^a is or contains a $-P(=O)(R^3)_2$ group. Examples of R^a containing a $-P(=O)(R^3)_2$ group include, without limitation, $-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-P(=O)(R^3)_2$, $-(CH_2)_m-O-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-C(O)O-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-C(O)-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-C(O)NR^1-(CH_2)_m-P(=O)(R^3)_2$ in which m is 0, 1, 2, 3 or 4.

Illustrative examples of this class are the following compounds of Formula IA:

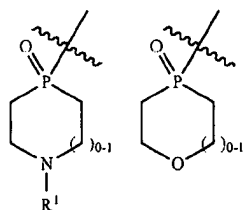


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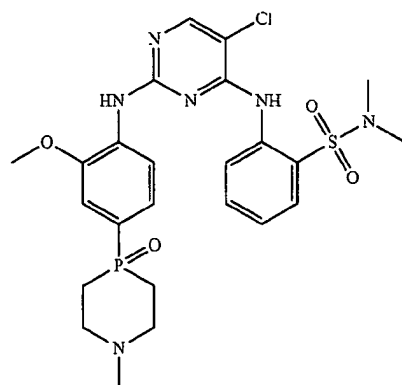
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In certain embodiments, R^a contains a $-P(=O)(R^3)_2$ substituent as part of a cyclic structure. For example, two R^3 groups can combine to form a ring system including a phosphorous atom, wherein the ring system is a 5-, 6- or 7-membered saturated ring, optionally substituted; and which can optionally contain one heteroatom selected from N, O and S(O). In certain embodiments, R^a is or contains a group described by one of the following formulas:

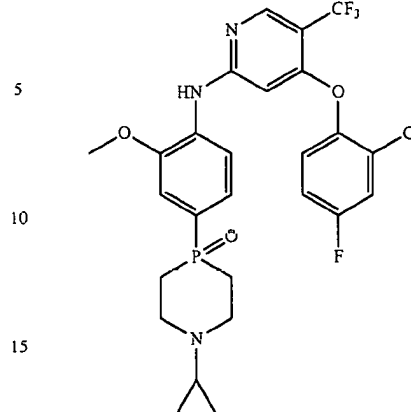


Illustrative examples of this class are compounds of Formula Ia include:

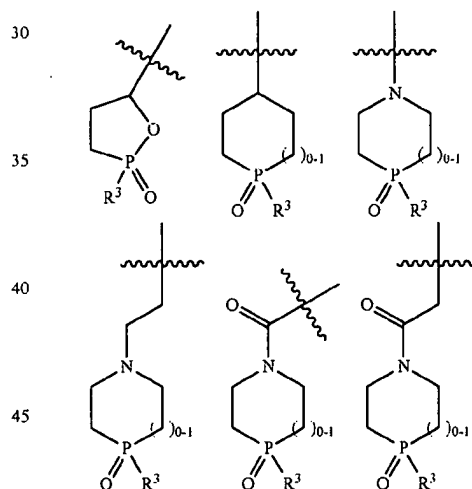


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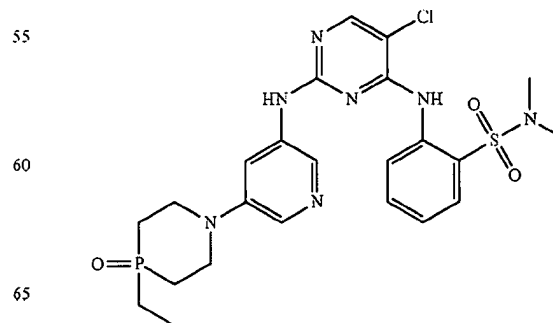
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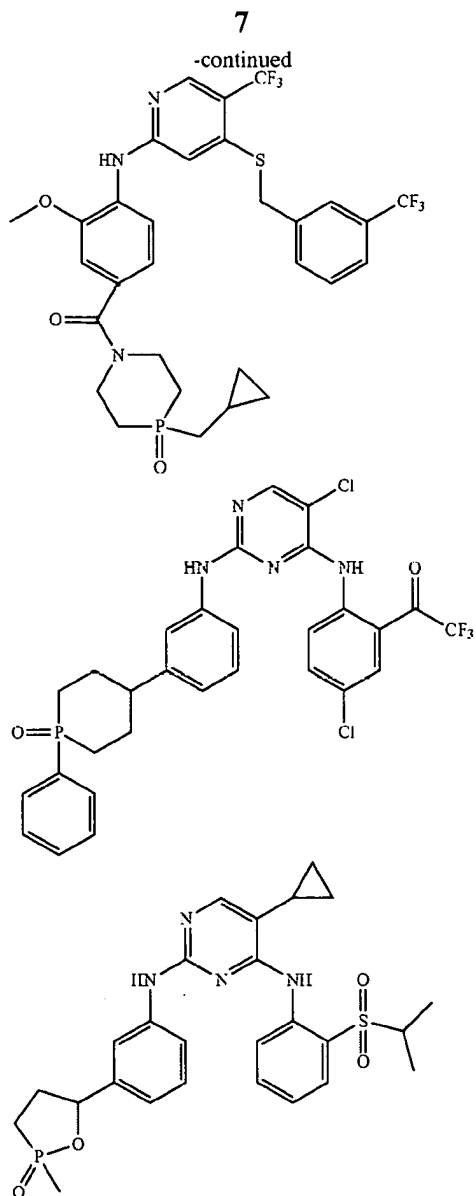


In other cases, R^a is a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member, such as a 5-, 6- or 7-membered saturated ring, optionally substituted; which contains a phosphorous atom and can optionally contain 1 heteroatom selected from N, O and S(O). In certain embodiments, R^a is or contains a group described by one of the following formulas:

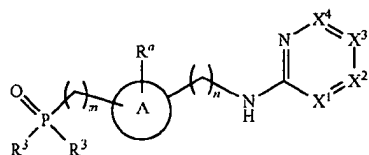


Illustrative examples of this class are compounds of Formula Ia include:





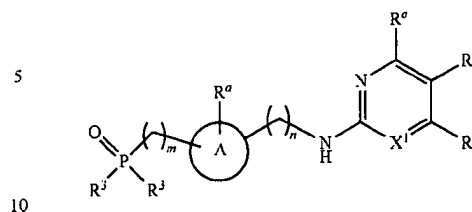
In one subclass of interest, one of R^a is $-(CH_2)_m-$, $-P(=O)(R^3)_2$. This class is illustrated by compounds of Formula II.



in which variables R^3 , R^a , n , Ring A, X^1 , X^2 , X^3 and X^4 are as defined above in Formula I and m is 0, 1, 2, 3 or 4.

One class of compounds which is of special interest for use in the invention are compounds of Formula II, as described above, in which X^2 is CR^c , X^3 is CR^d and X^4 is CR^e . This class is illustrated by compounds of Formula IIA:

Formula IIA



in which variables R^3 , R^a , Ring A, n , X^1 , R^c , R^d , and R^e are as defined above in Formula I and m is 0, 1, 2, 3 or 4.

In one subclass of interest are compounds of Formula II or IIA in which m is 0. In another subclass m is 1.

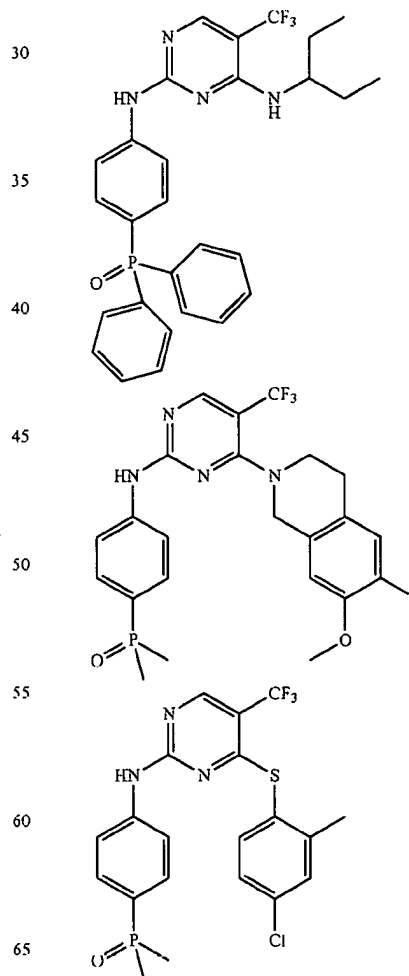
In another subclass of interest are compounds of Formula II or Formula IIA in which X is N.

In another subclass of interest are compounds of Formula II or Formula IIA in which X is CR^b .

In another subclass of interest are compounds of the above classes and subclasses in which n is 0. In another subclass n is 1.

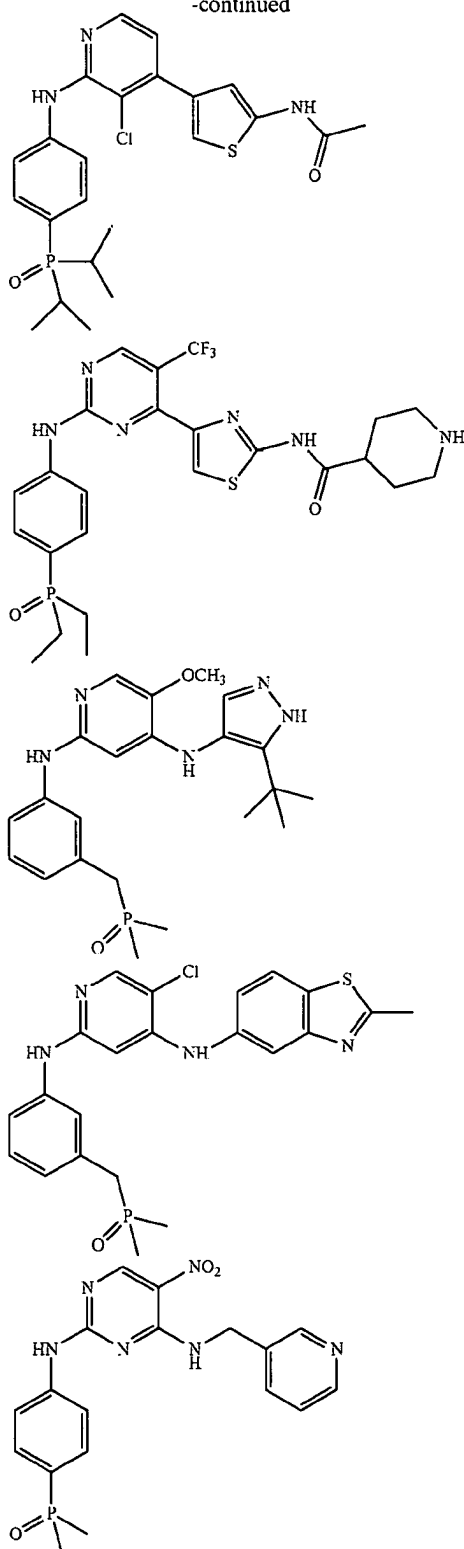
One class of compounds of special interest are compounds of Formula IIA in which Ring A is a phenyl.

Non limiting examples of this embodiment include the following compounds of Formula IIA:



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In one embodiment, two adjacent substituents selected from R^{c1} , R^{d1} , R^e and R^f form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring B, which is substituted with 1 to 4

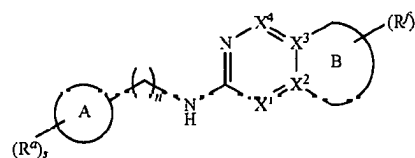
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R^f ; and which contains 0-4 heteroatoms selected from N, O and S(O)_r. This class is illustrated by compounds of Formula III:

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Formula III

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15 in which variables R^a , R^f , Ring A, n, s, X^1 , X^2 , X^3 and X^4 are as described in Formula I; and t is 1, 2, 3 or 4.

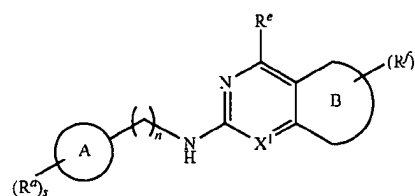
One class of compounds which is of special interest for use in the invention are compounds of Formula III, as described above, in which X^2 is CR^c , X^3 is CR^d and X^4 is CR^e and R^c and R^d moieties form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring B. This class is illustrated by compounds of Formula IIIA:

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Formula IIIA

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in which variables R^a , X^1 , Ring A, n, s, t, X^1 , R^e and R^f are as described in Formula III.

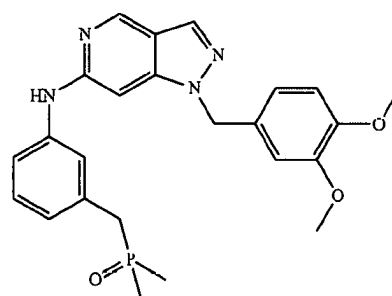
In one particular embodiment, one R^a is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member (i.e. $(CH_2)_mP(=O)(alkyl)_2$, in which m is 0, 1, 2, 3 or 4 and other examples of phosphorous containing substituents, including cyclic ones as listed above). In another particular embodiment, R^f is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member (i.e. $(CH_2)_mP(=O)(alkyl)_2$, in which m is 0, 1, 2, 3 or 4 and other examples of phosphorous containing substituents, including cyclic ones as listed above).

One class of compounds of special interest are compounds of Formula III or IIIA in which Ring A is a phenyl.

Illustrative examples of this class are the following compounds of Formula IIIA:

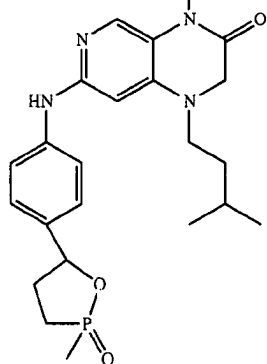
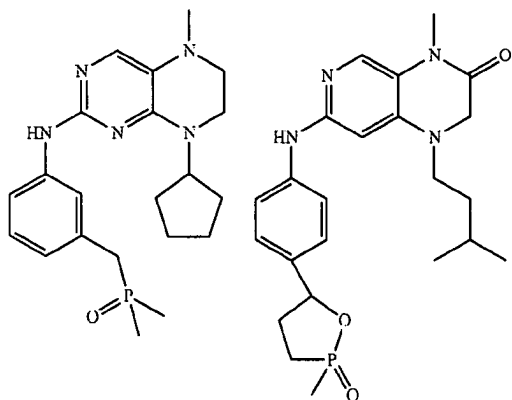
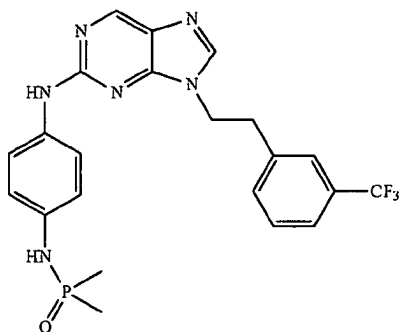
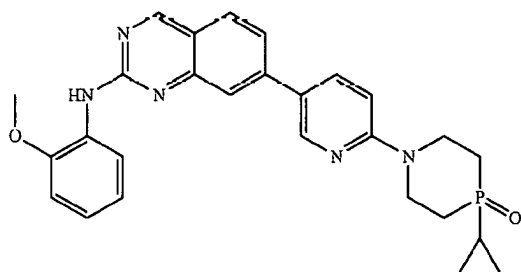
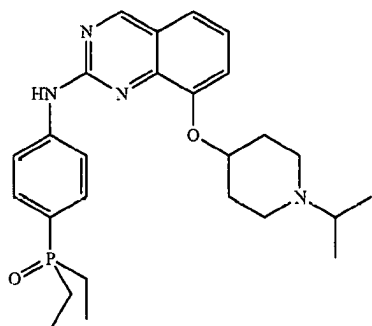
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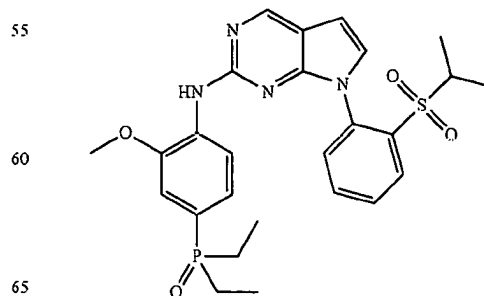
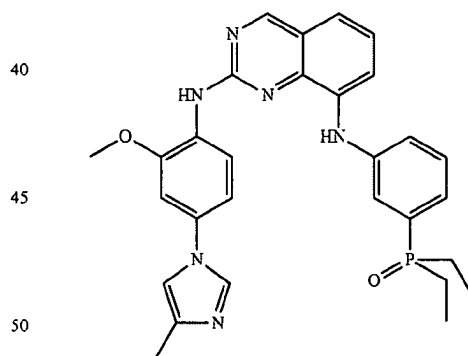
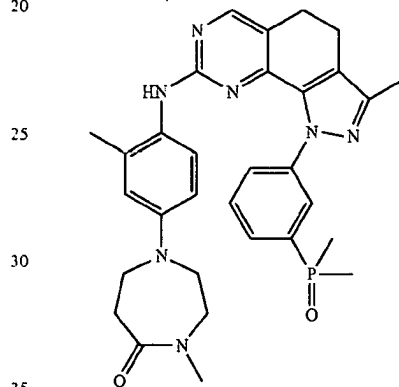
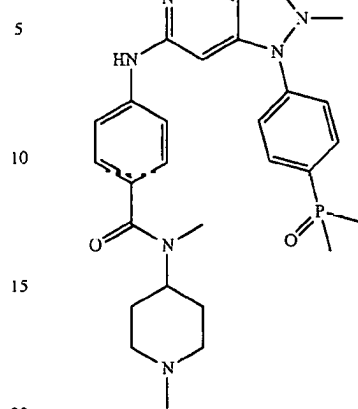


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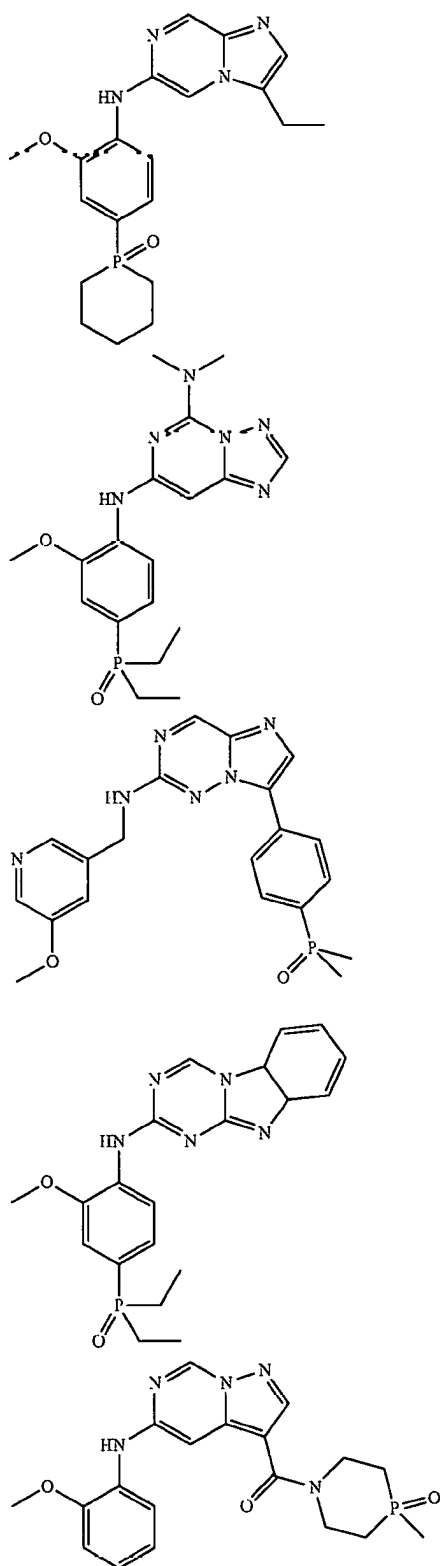
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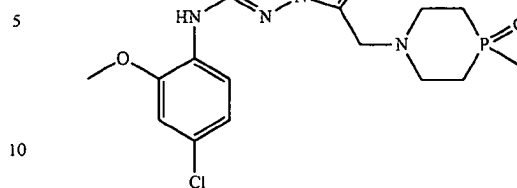
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Other Illustrative examples of this class are the following compounds of Formula III:



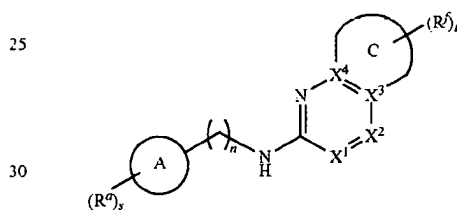
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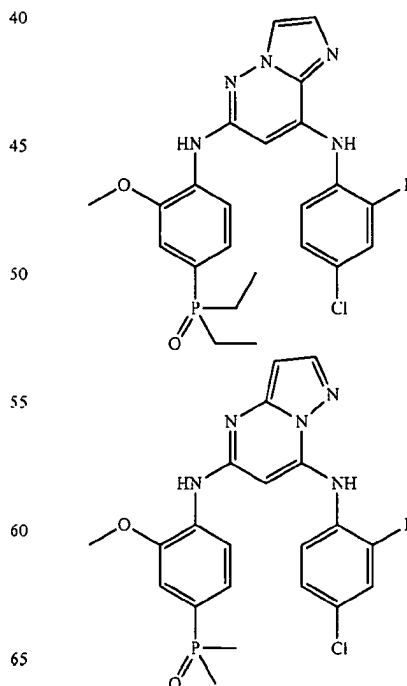
In another embodiment, two adjacent substituents selected from R^{d1} , R^{e1} , $R^{d'}$ and $R^{e'}$ form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring C, which is substituted with 1 to 4 R^f ; and which contains 0-4 heteroatoms selected from N, O and S(O)_n. This class is illustrated by compounds of Formula IV:

Formula IV

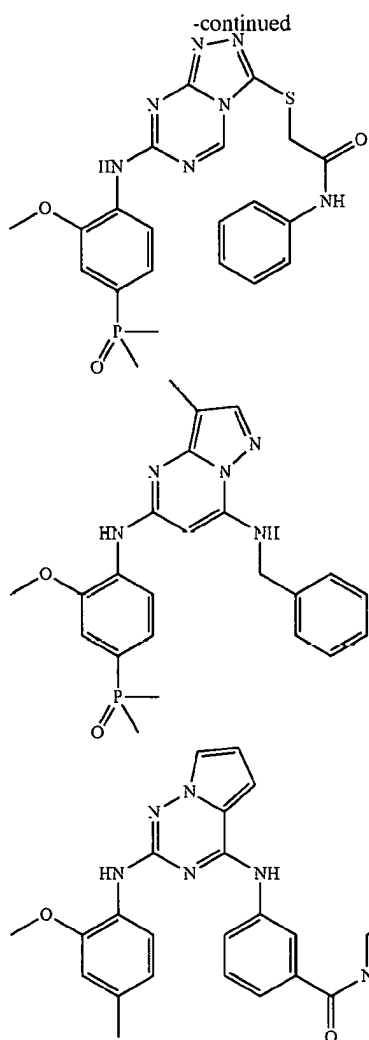


in which Ring A, R^d , R^e , R^f , R^g , n , X^1 , X^2 , X^3 and X^4 are as defined in Formula I; and t is 1, 2, 3 or 4.

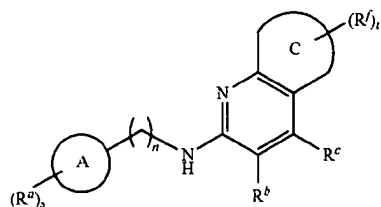
Illustrative examples of this class are the following compounds of Formula IV:



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One class of compounds which is of special interest for use in the invention are compounds of Formula IV, as described above, in which X^1 is CR^d , X^2 is CR^c , X^3 is CR^d and X^4 is CR^e and R^d and R^e moieties form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring C. This class is illustrated by compounds of Formula IVA:



in which Ring A, Ring C, R^a , s , n , R^b , R^c , R^d and t are as defined above in Formula IV.

In one particular aspect of this embodiment, one R^a is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member.

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In another aspect of this embodiment, one of R^c is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member.

5 In another aspect of this embodiment, R^c is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member.

One class of compounds of special interest are compounds of Formula IV or IVA in which Ring A is a phenyl.

10 Illustrative examples of this class are the following compounds of Formula IVA:

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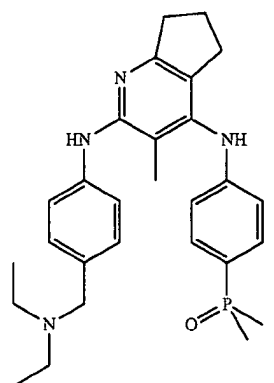
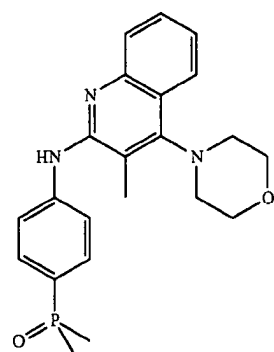
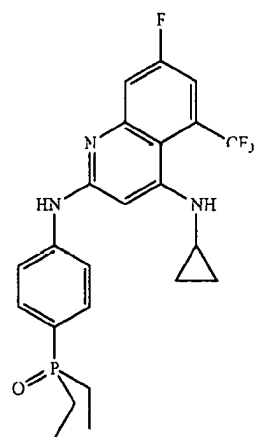
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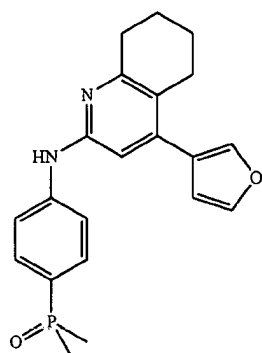
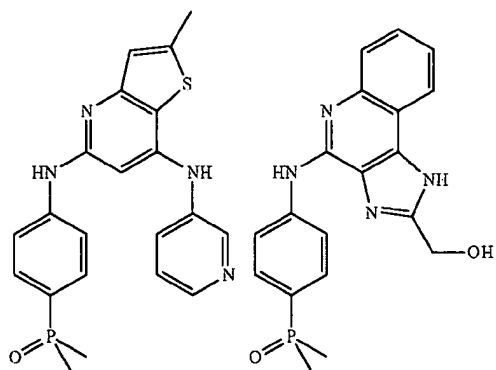
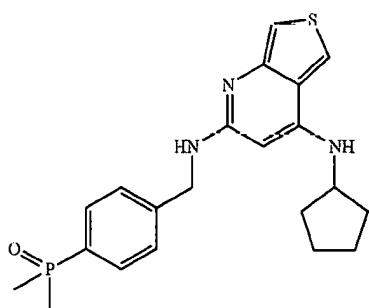
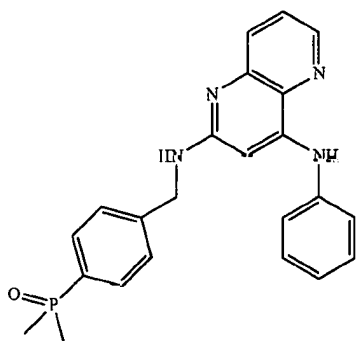
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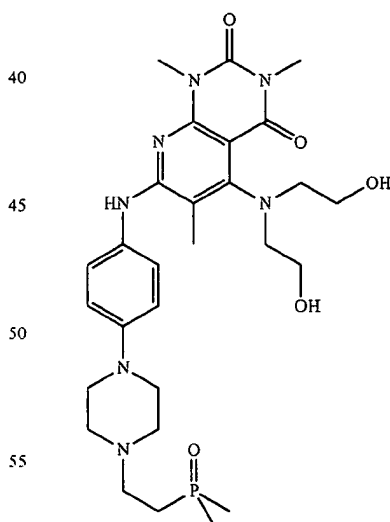
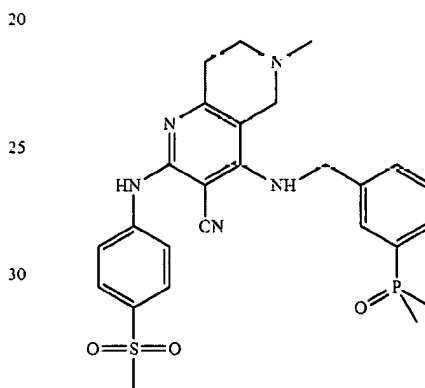
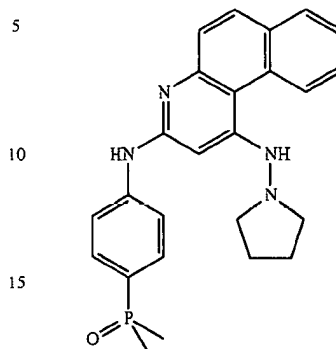
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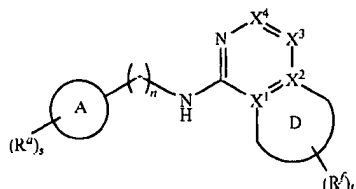
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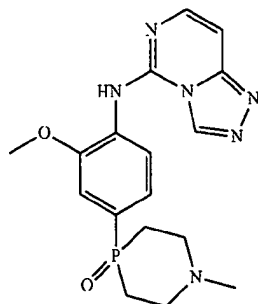
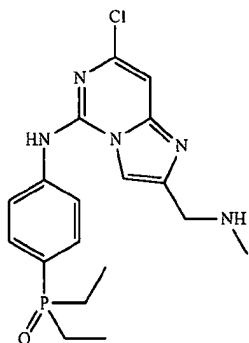
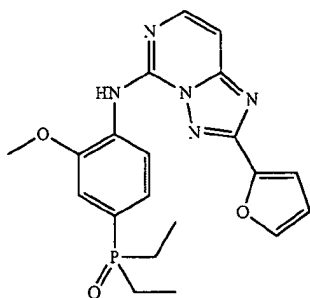
60 In another embodiment, two adjacent substituents selected from R^b , R^c , R^{b1} and R^{c1} form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring D, which is substituted with 1 to 4 R^f groups; and which contains 0-4 heteroatoms selected from N, O and S(O)_n. This class is illustrated by compounds of Formula V:

19



in which R^a , s , n , X^1 , X^2 , X^3 , X^4 and R^f are as defined above in Formula I; and t is 1, 2, 3 or 4.

Illustrative examples of this class are the following compounds of Formula V:



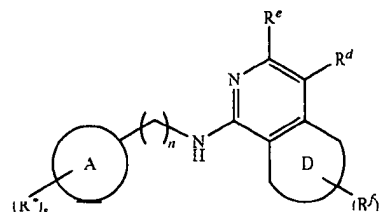
One class of compounds which is of special interest for use in the invention are compounds of Formula V, as described above, in which X^1 is CR^b , X^2 is CR^c , X^3 is CR^d and X^4 is CR^e and R^b and R^c form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring D. This class is illustrated by compounds of Formula VA:

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Formula V

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Formula VA

in which R^a , s , n , t , Ring A, Ring D, R^d , R^e and R^f are as defined above in Formula V.

In one particular aspect of this embodiment, one R^e is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member.

In another aspect of this embodiment, one of R^f is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member.

One class of compounds of special interest are compounds of Formula V or VA in which Ring A is a phenyl.

Illustrative examples of this class are the following compounds of Formula VA:

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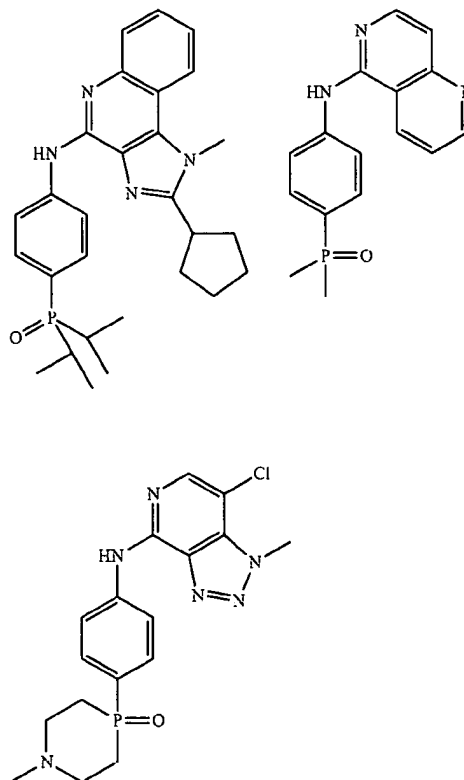
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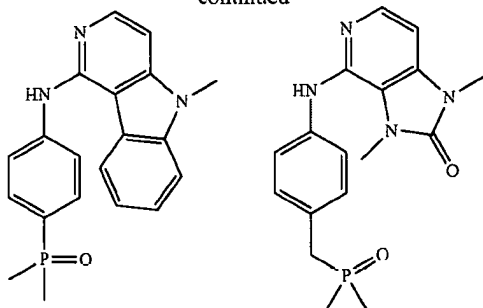
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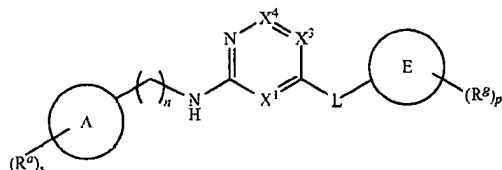
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The invention also features compounds of Formula VI:

Formula VI



wherein

X^1 is NR^{b1} or CR^b ;

X^3 is NR^{d1} or CR^d ;

X^4 is NR^{e1} or CR^e ;

Ring A is an aryl, a 5- or a 6-membered heteroaryl ring which contains 1 to 4 heteroatoms selected from N, O and S(O);

Ring E represents an aryl, a carbocyclyl or a 5-, 6- or 7-membered heterocyclic or heteroaryl ring comprising carbon atoms and 1-4 heteroatoms independently selected from O, N and S(O); Ring E is optionally fused with a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring and Ring E is substituted on carbon or on the heteroatom(s) with 1-7 R^g groups.

L is a bond, $O(CH_2)_y$, $NR^4(CH_2)_y$, $S(O)_r(CH_2)_y$, $(CH_2)_y$, $(CH_2)_ySO_2NR^4$, $(CH_2)_yNR^4SO_2$, $(CH_2)_yCH=CH$, $(CH_2)_yC=C$, $(CH_2)_y$



$(CH_2)_yC(O)NR^4$, $(CH_2)_yNR^4C(O)$; y is 0, 1, 2, 3 or 4; p is 1, 2, 3, 4, 5, 6 or 7; r is 0, 1 or 2, R^4 is H or alkyl; and the linker L can be included in either direction.

at each occurrence R^a , R^b , R^d and R^e are independently selected from the group consisting of halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^{3a})_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$, and R^{b1} , R^{d1} and R^{e1} are absent; wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$; or

alternatively two adjacent substituents selected from R^b , R^{b1} , R^d , R^{d1} , R^e and R^{e1} ; or two adjacent R^a moieties, can

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form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4 heteroatoms selected from N, O and S(O), and which is substituted with one to four R^f moieties wherein;

each R^f moiety is independently selected from the group consisting of halo, $=O$, $=S$, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^{3a})_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; or alternatively two adjacent R^f moieties can form with the atoms to which they are attached a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, optionally substituted; and which contains 0-4 heteroatoms selected from N, O and S(O);

each R^g moiety is independently selected from the group consisting of halo, $=O$, $=S$, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^{3a})_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$; and at least one of R^a , R^b , R^d , R^e or R^g , when present, is or contains $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member;

r is 0, 1 or 2;

s is 1, 2, 3, 4 or 5

n is 0 or 1;

p is 1, 2, 3 or 4;

each occurrence of Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$;

each occurrence of R^1 and R^2 is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic and heteroaryl;

each occurrence of R^3 is independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic and heteroaryl, or two adjacent R^3 moieties combine to form a ring system including a phosphorous atom;

each occurrence of R^{3a} is independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic, and heteroaryl;

alternatively, each NR^1R^2 moiety may be a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which can be optionally substituted and which contains 0-2 additional heteroatoms selected from N, O and S(O); and

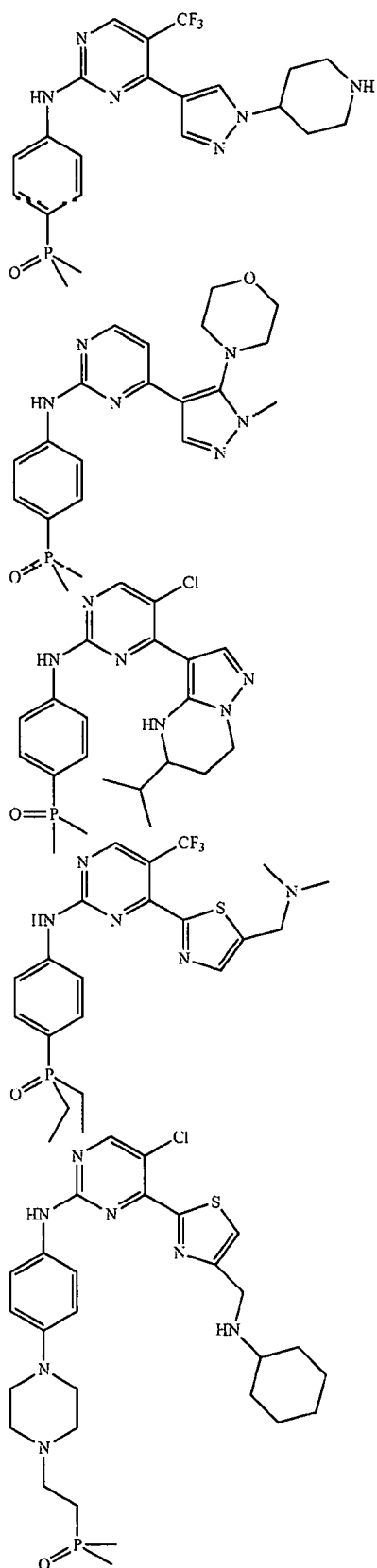
each of the foregoing alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocyclic moiety is optionally substituted.

In one embodiment are compounds of Formula VI in which one of R^a is or contains $-P(=O)(R^3)_2$.

In another embodiment are compounds of Formula VI in which one of R^g is or contains $-P(=O)(R^3)_2$.

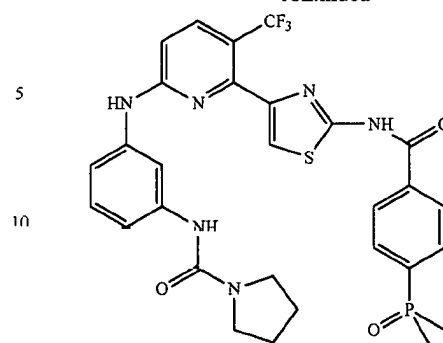
In one embodiment are compounds of formula VI in which L is a bond. Non-limiting examples of this class include the following compounds:

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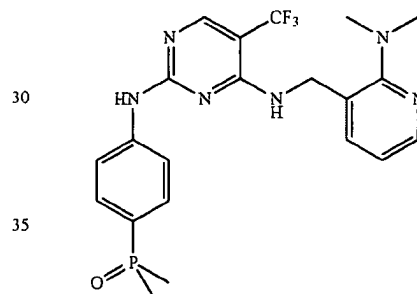
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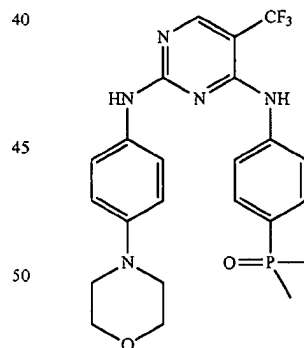


In another embodiment are compounds of formula VI in which L is NR⁴(CH₂)_y. In a particular aspect, L is NR⁴. In another particular aspect, L is NR⁴(CH₂)₁₋₃. Non-limiting examples of L linker are NHCH₂CH₂, NHCH₂, NH and NCH₃. Non limiting examples of this class include the following compounds:

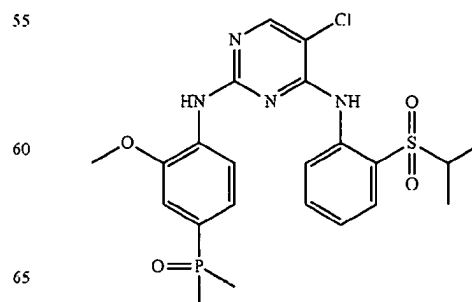
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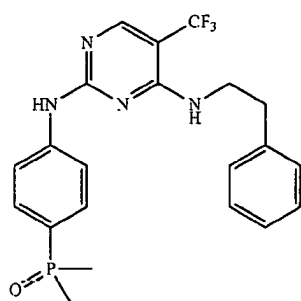
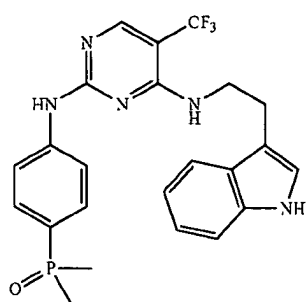
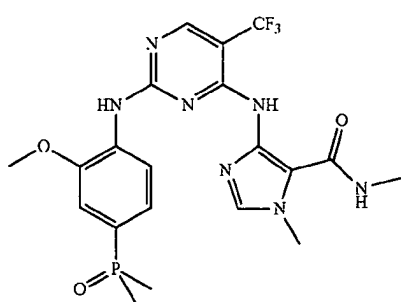
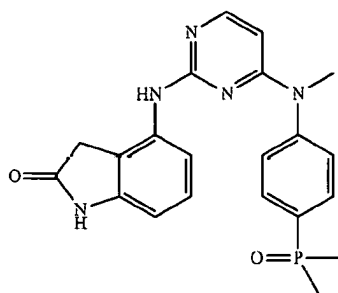
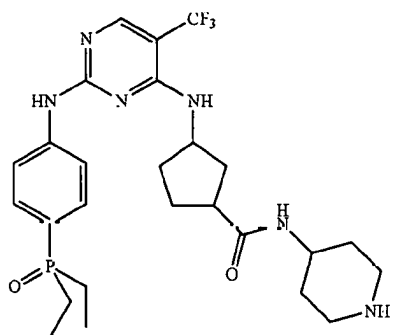


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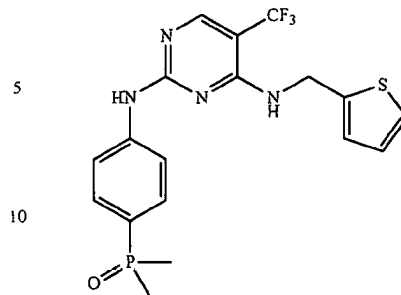
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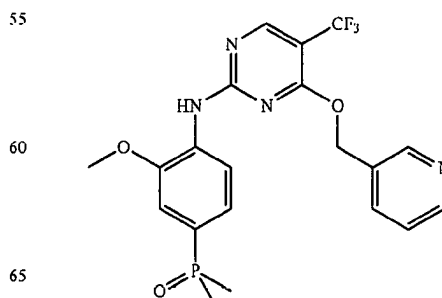
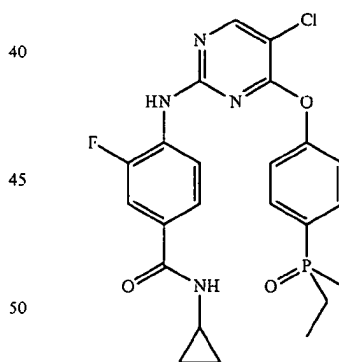
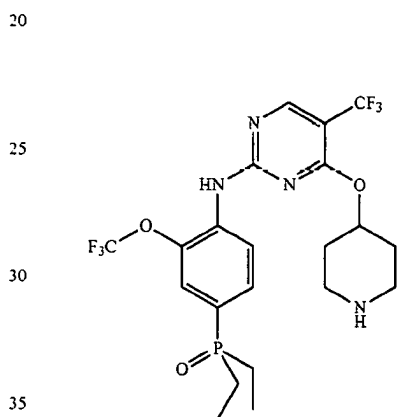


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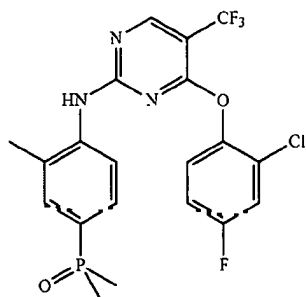


15 In another embodiment are compounds of formula VI in which L is $O(CH_2)_v$. Non limiting examples of this class include the following compounds:

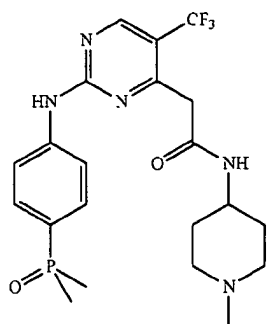
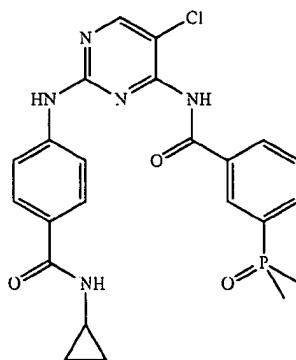
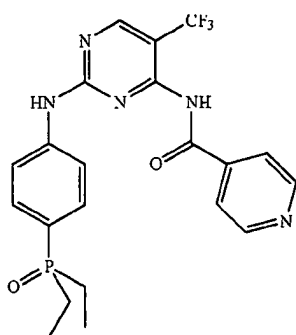


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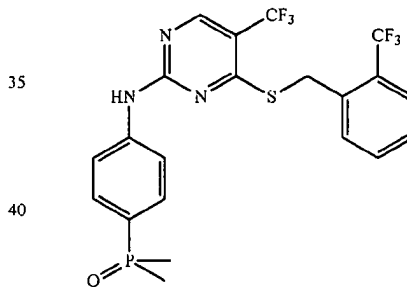
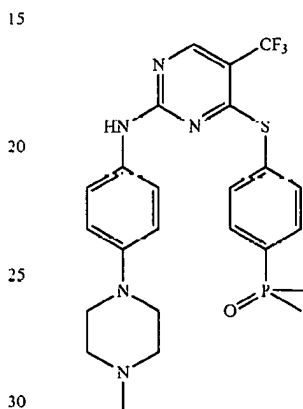
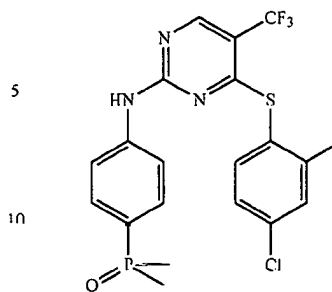


In another embodiment are compounds of Formula VI in which L is $(\text{CH}_2)_2\text{C}(\text{O})\text{NR}^4$ or $(\text{CH}_2)_2\text{NR}^4\text{C}(\text{O})$. Non limiting examples of this class include the following compounds:

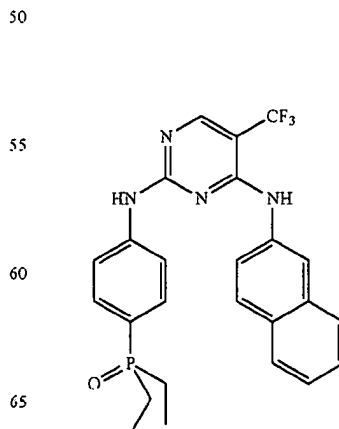


In another embodiment are compounds of formula VI in which L is $\text{S}(\text{CH}_2)_2$. Non limiting examples of this class include the following compounds:

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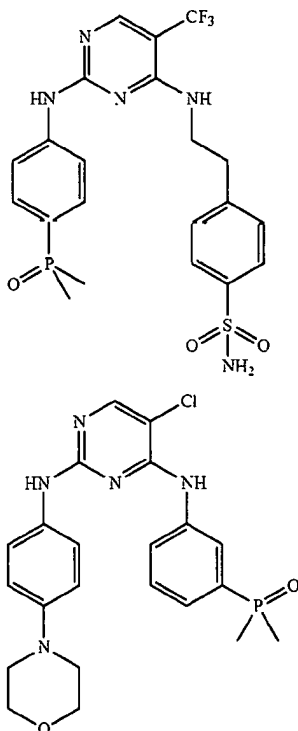


In still another embodiment are compounds of Formula VI in which Ring E is an aryl, substituted with 1 to 5 R^8 groups. Non-limiting examples of this class are compounds of the following types:

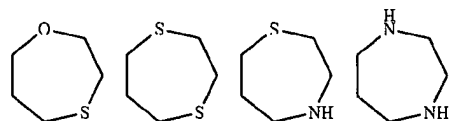
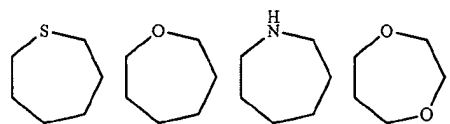
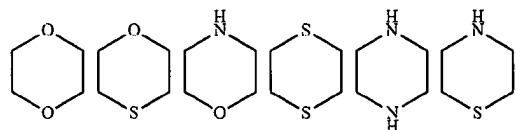
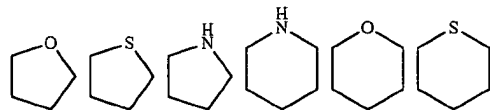
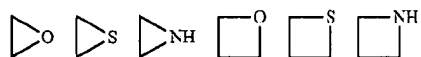


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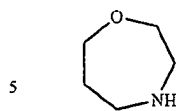


In another embodiment are compounds of Formula VI in which Ring E is a 5-, 6- or 7-membered heterocyclyl ring comprising carbon atoms and 1-3 heteroatoms independently selected from O, N and S(O)_n, and Ring E is substituted on carbon or on the heteroatom(s) with 1-7 R^g groups. It is understood that the total number of substituents R^g does not exceed the normal available valencies. Non-limiting examples of this class are compounds of formula VI in which Ring E is of the following types:

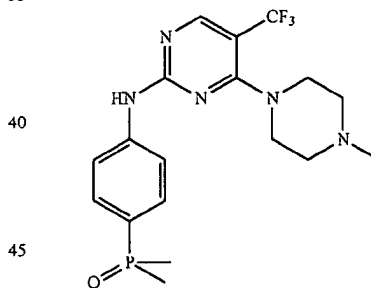
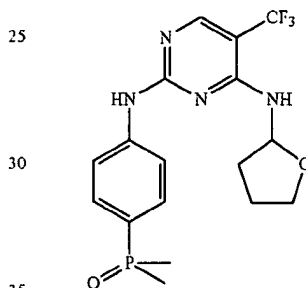
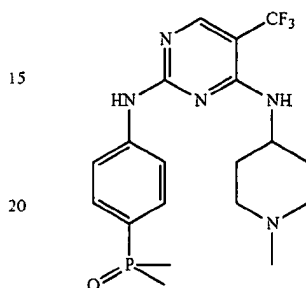


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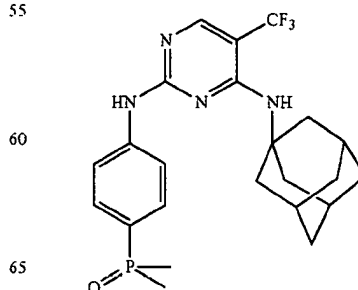
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Non-limiting illustrative examples are compounds of the following formulae:

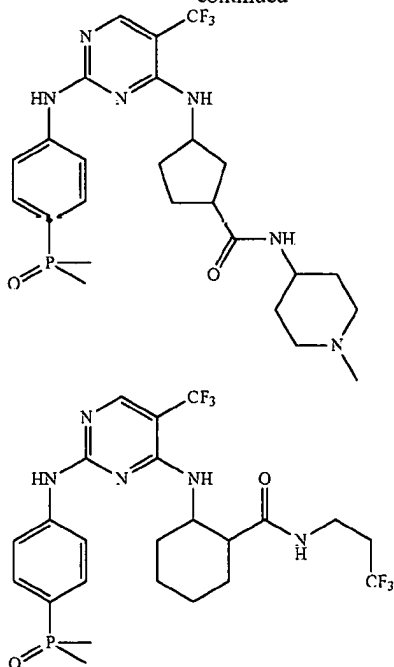


In another embodiment are compounds of Formula VI in which Ring E is a carbocyclyl ring and Ring E is substituted with 1-7 R^g groups. Non-limiting examples of this class are compounds of the following types:



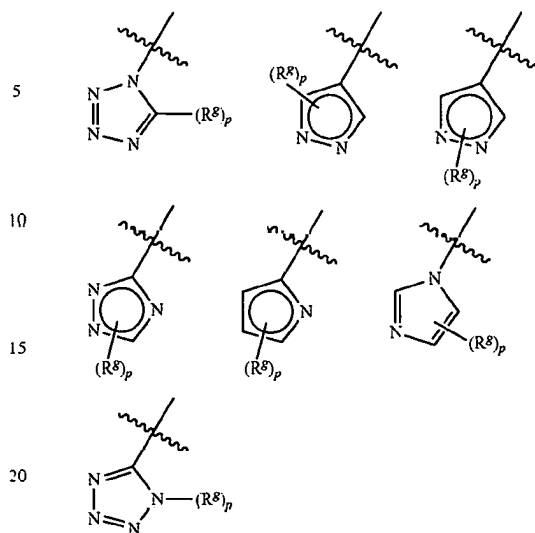
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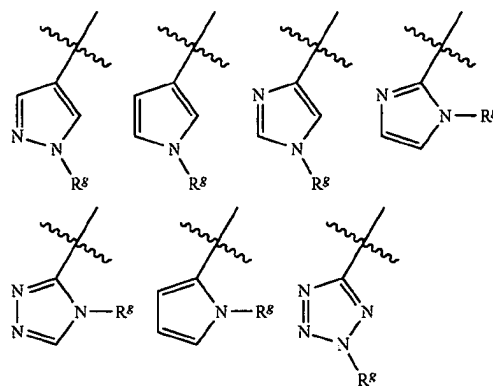
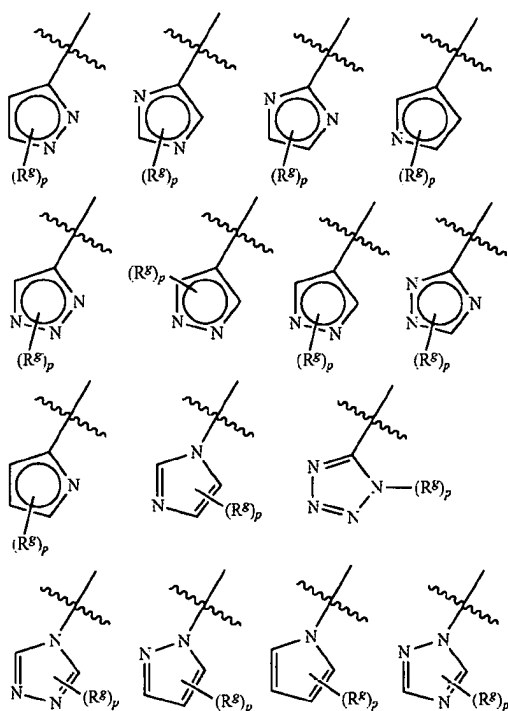
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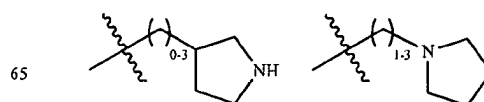
25 In certain embodiments, Ring E has the following formulae:

In another aspect of the previous embodiment, Ring E is a 5-, 6- or 7-membered heteroaryl ring comprising carbon atoms and 1-3 heteroatoms independently selected from O, N and S(O)_r. For example, Ring E can be a 5-membered ring heteroaryl comprising carbon atoms and 1-3 Nitrogen atoms. Non-limiting examples of this class are compounds in which Ring E is of the following types:



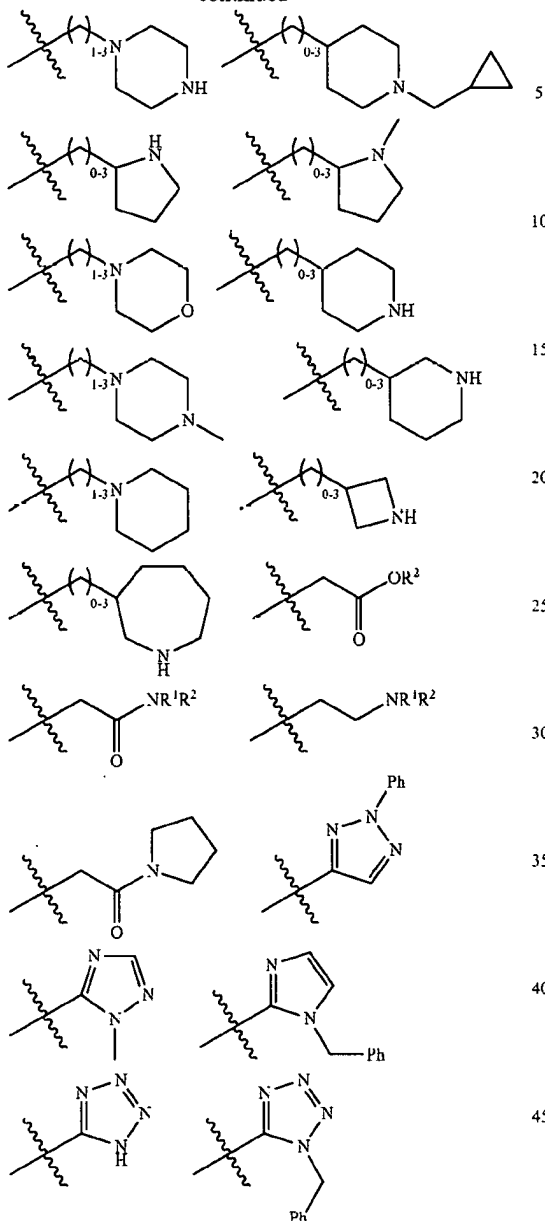
Of additional interest is a class of compounds as described above in which R^g is selected from the group consisting of —R¹ and —C(O)YR². In another subclass of interest, are compounds of the above embodiment in which R^g is an aryl, heteroaryl, substituted alkyl or heterocyclyl. Non limiting examples of substituted alkyl are —(CH₂)_zC(=O)NR¹R², —(CH₂)_zNHC(=O)R², —(CH₂)_zNR¹R², —(CH₂)_zC(=O)OR¹, —(CH₂)_zheterocyclyl, —(CH₂)_z aryl, —(CH₂)_zheteroaryl in which z is 1, 2, 3 or 4 and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

Illustrative examples of such Ring E groups including substituent R^g include, without limitation:

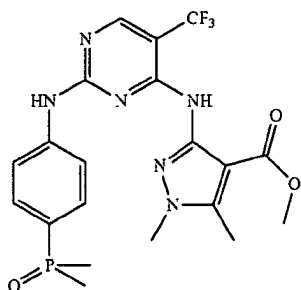


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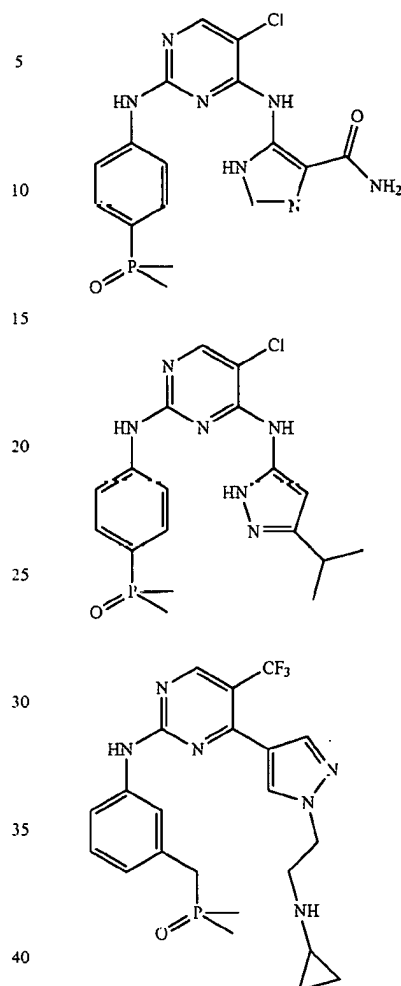


Non-limiting Illustrative examples of this class are compounds of the following formulae:



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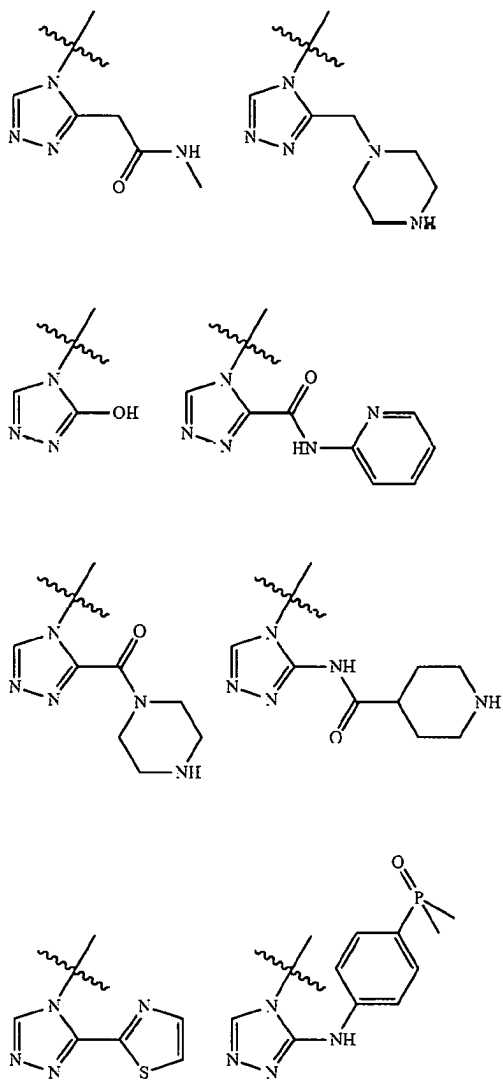


In another embodiment, Ring E is a 5-membered ring
45 heteroaryl comprising carbon atoms and 1-3 Nitrogen atoms
and the heteroaryl ring is linked to the core moiety via a
nitrogen atom. In one preferred aspect of this embodiment L
is a bond or (CH₂)_n.

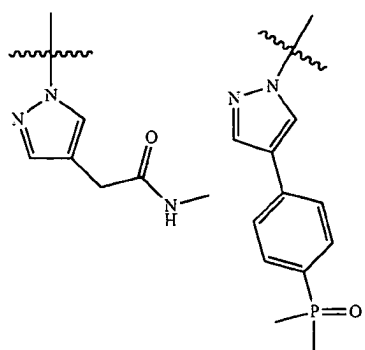
Of additional interest is a class of compounds as described above in which R^8 is selected from the group consisting of $-R^1$, $-OR^2$, $-P(=O)(R^3)_2$, $-NR^1R^2$, $-C(O)YR^2$, $-NR^1C(O)YR^2$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$. In another subclass of interest, are compounds of the above embodiment in which R^8 is an aryl, heteroaryl, substituted alkyl or heterocyclyl. Non limiting examples of R^8 are $-(CH_2)_yC(=O)NR^1R^2$, $-(CH_2)_yNHC(=O)R^2$, $-(CH_2)_yNR^1R^2$, $-(CH_2)_y$ heterocyclyl, $-(CH_2)_y$ aryl, $-(CH_2)_y$ heteroaryl, NI -aryl, NI -heteroaryl and NH -heterocyclyl; in which y is 0, 1, 2, 3 or 4 and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

65 Illustrative non limiting examples of such compounds include compounds of Formula VI in which Ring E is a triazole of the following formulae:

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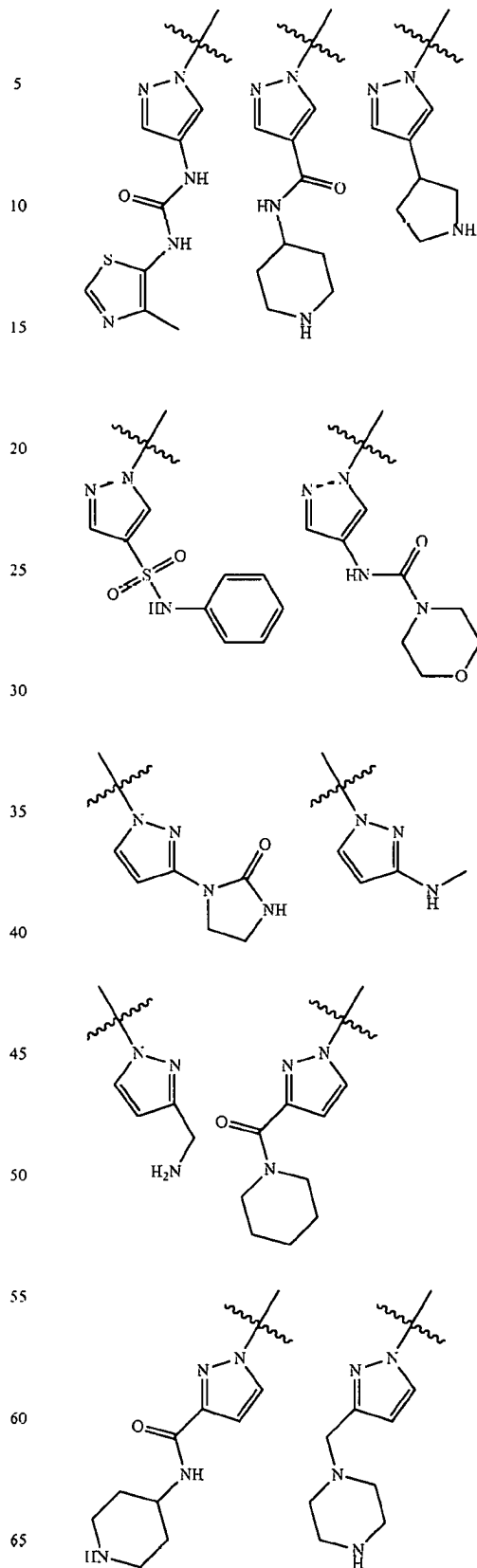


In another embodiment, Ring E is a pyrazole of the following formulae:



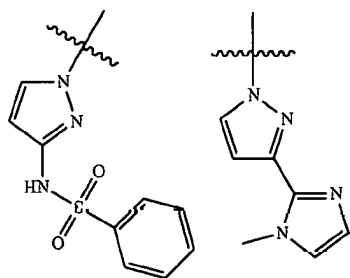
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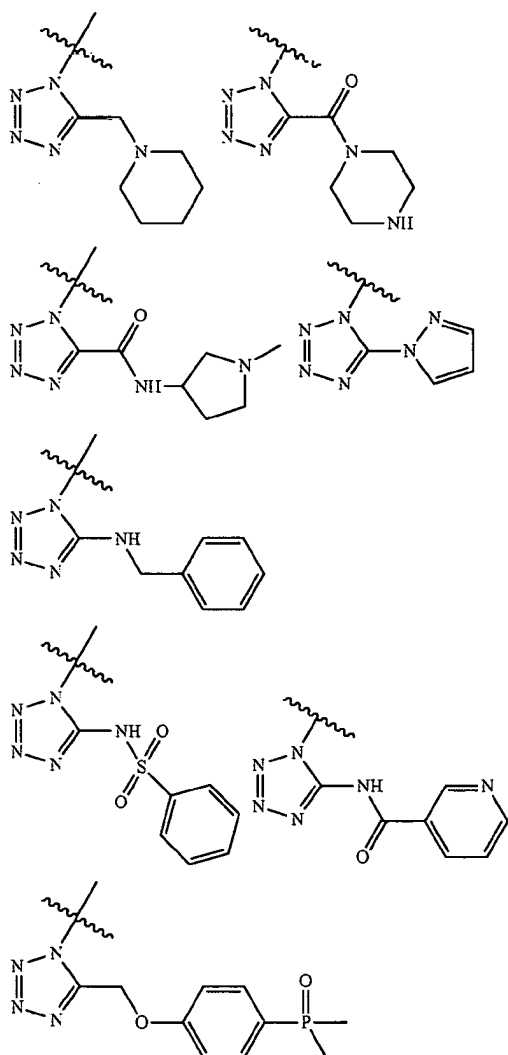


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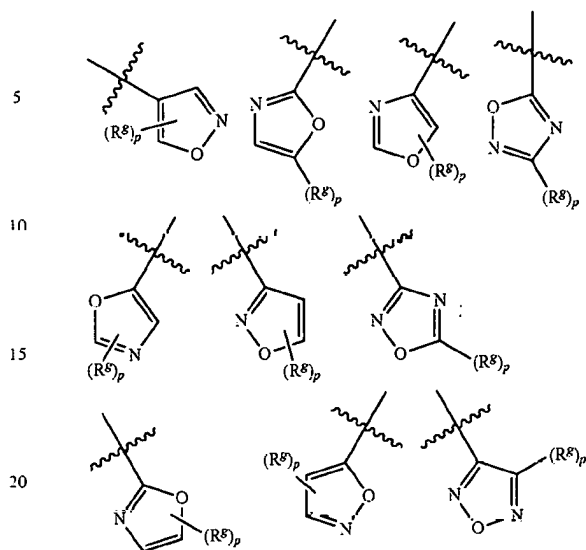


In another aspect of the previous embodiment, Ring E is a tetrazole of the following formulae:



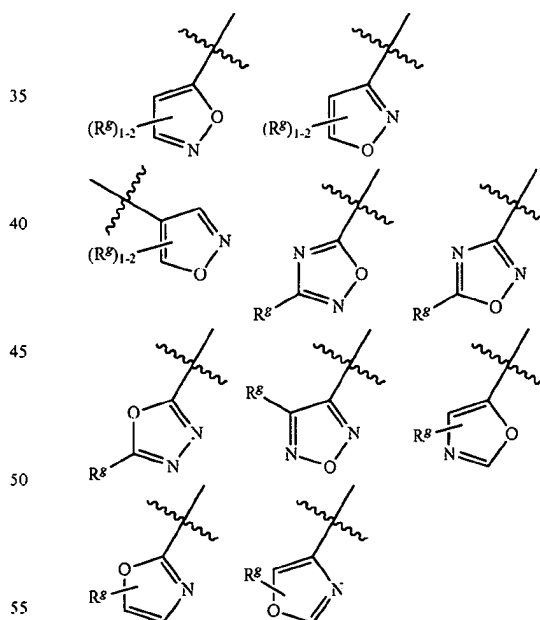
In another embodiment, Ring E is a 5-membered ring heteroaryl comprising carbon atoms and 1-3 heteroatoms selected from N and O. Non limiting examples are compounds of formula VI in which Ring E is of the following type:

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in which p is defined previously and the total number of substituents R^g does not exceed the normal available valencies.

In certain particular embodiments, Ring E has the following formulae:



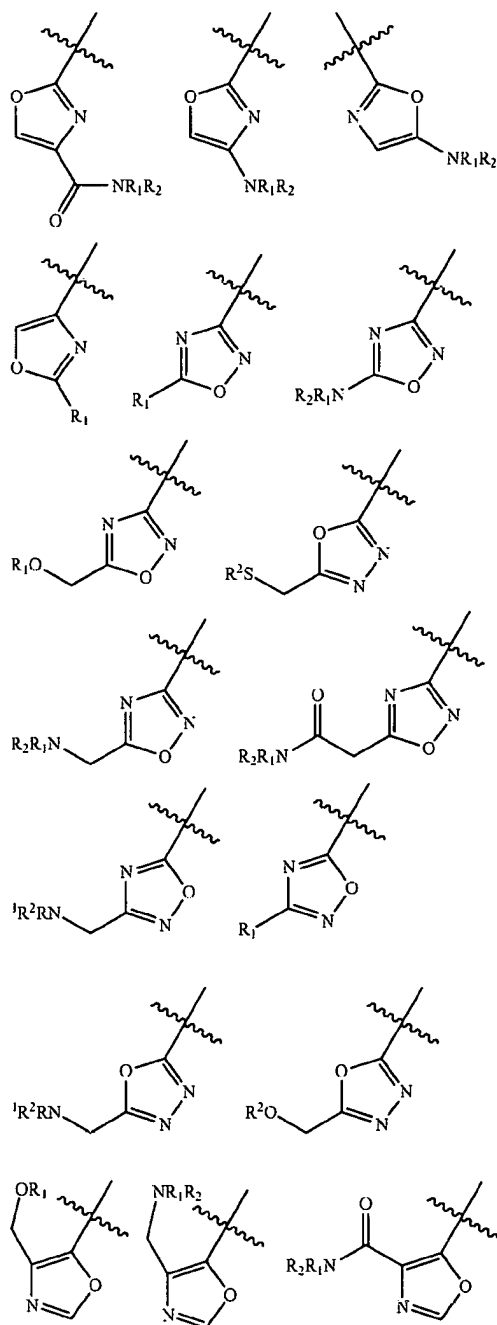
in which Ring E is substituted with one or two R^g substituents.

Of additional interest is a class of compounds as described above in which R^g is selected from the group consisting of $-R^1$, $-P(=O)(R^3)_2$, $-OR^2$, $-NR^1R^2$, $-C(O)YR^2$, $-NR^1C(O)YR^2$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$. In another subclass of interest, are compounds of the above embodiment in which R^g is $NHC(O)R^1$, $NHC(O)NR^1R^2$, $C(O)NHR^1$, $C(O)NR^1R^2$, NR^1R^2 , an aryl, heteroaryl, substituted alkyl or heterocyclyl. Non limit-

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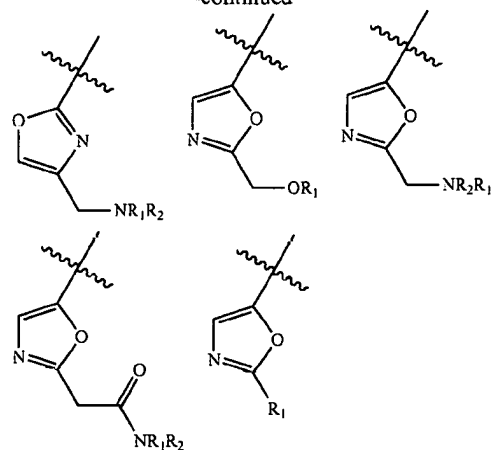
ing examples of R^g are $-(CH_2)_yC(=O)NR^1R^2$, $(CH_2)_yNHC(=O)R^2$, $(CH_2)_yNR^1R^2$, $(CH_2)_yOR^2$, $-(CH_2)_y$ heterocyclyl, $-(CH_2)_y$ aryl, $-(CH_2)_y$ heteroaryl, NH-aryl, NH-heteroaryl and NH-heterocyclyl, $-(CH_2)_mP(=O)(alkyl)_2$; in which y and m are independently selected from 0, 1, 2, 3 and 4 and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

Non-limiting examples of this class include compounds of formula VI in which Ring E is:

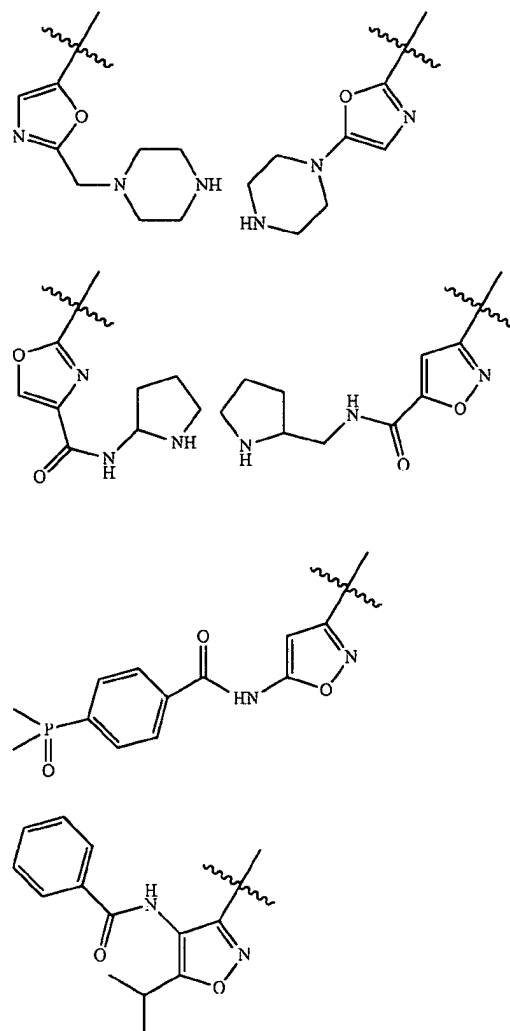


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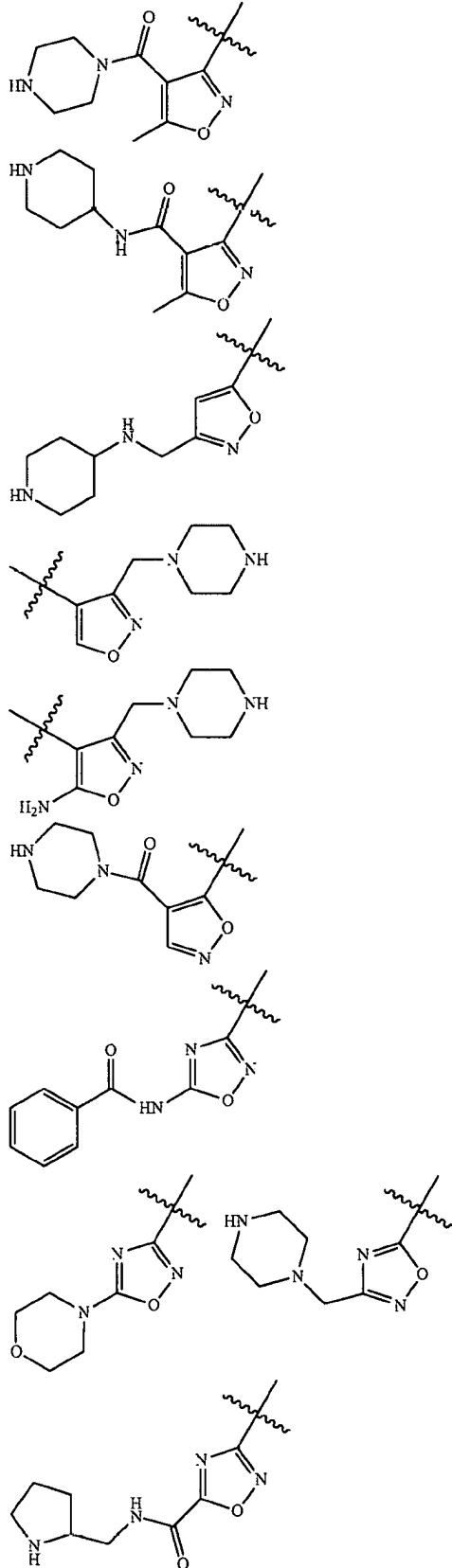


Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:



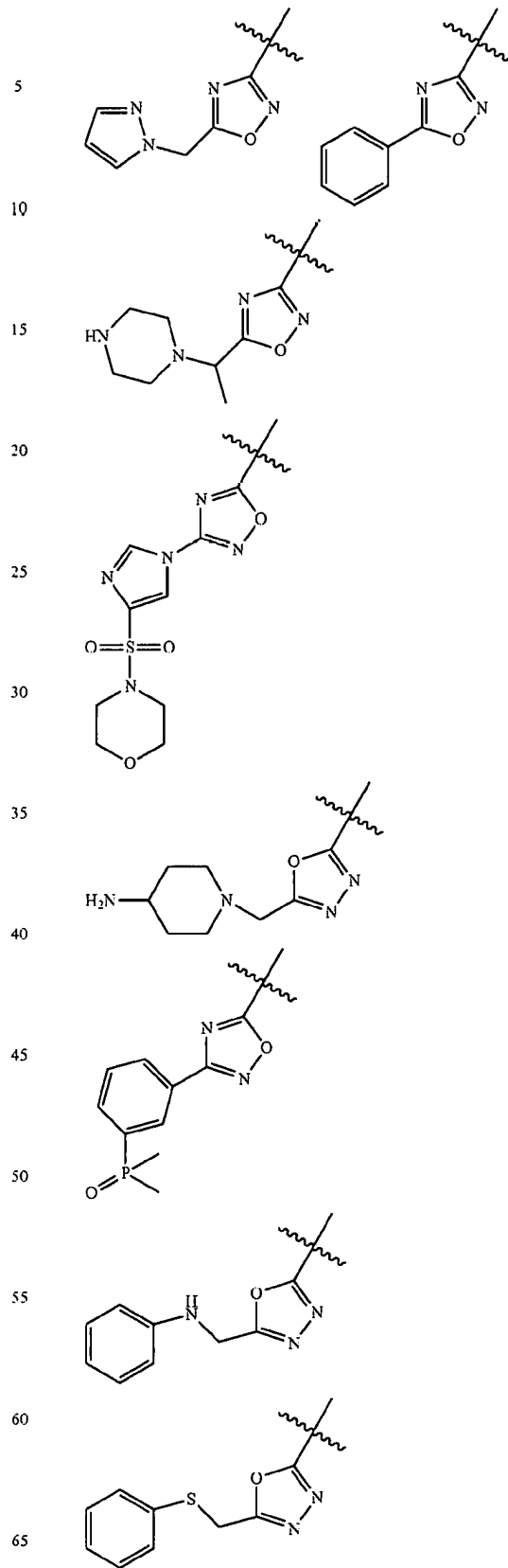
41

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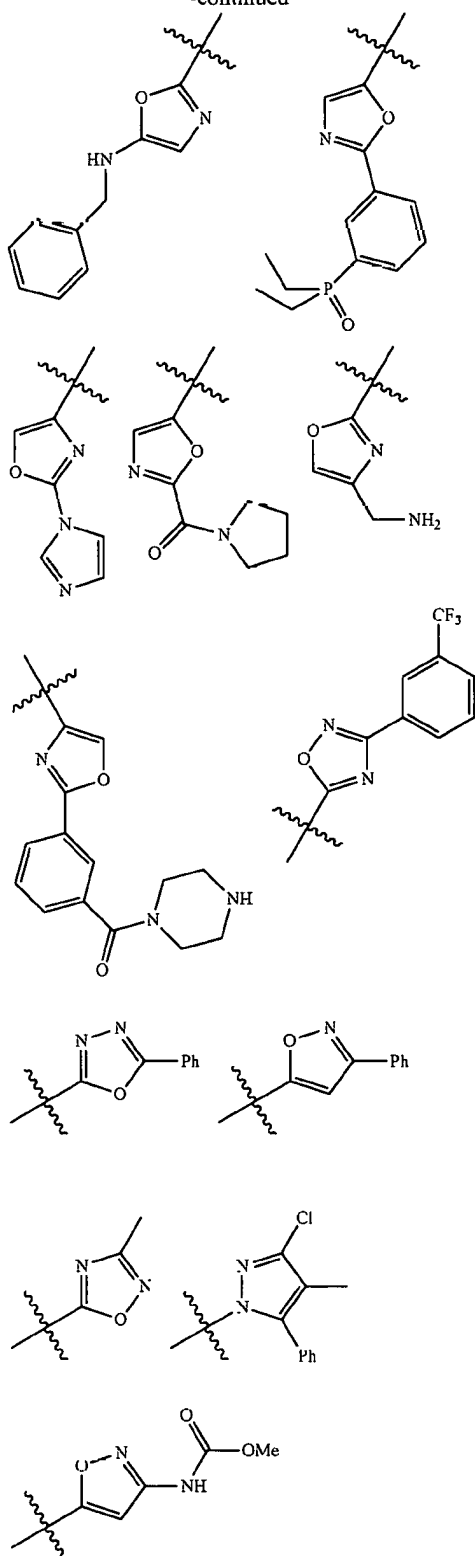
42

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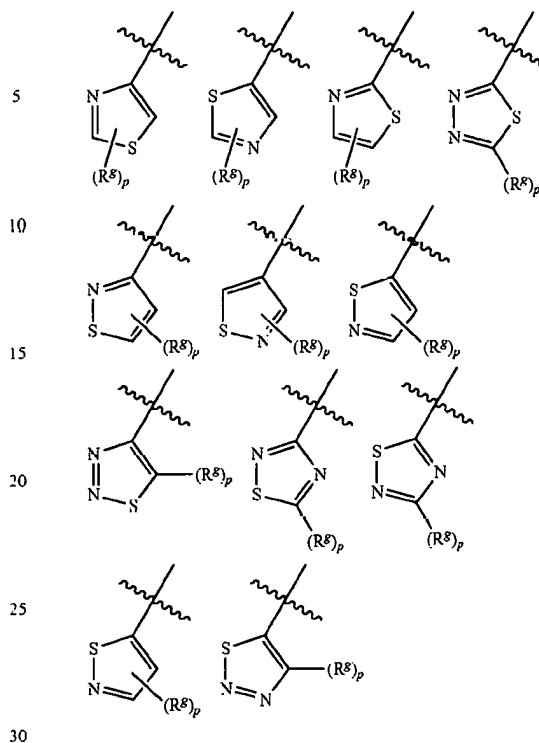


43

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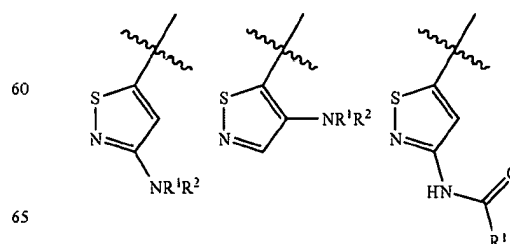
44



in which p is defined previously and the total number of substituents R^g does not exceed the normal available valencies.

Of particular interest is a class of compounds as described above in which R^g is selected from the group consisting of $-R^1$, $-P(=O)(R^3)_2$, $-OR^2$, $-NR^1R^2$, $-C(O)YR^2$, $-NR^1C(O)YR^2$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$. In another subclass of interest, are compounds of the above embodiment in which R^g is $NHC(O)R^1$, $C(O)NHR^1$, $C(O)NR^1R^2$, $NHC(O)NHR^1$, NR^1R^2 , an aryl, heteroaryl, substituted alkyl or heterocyclyl. Non limiting examples of R^g are $-(CH_2)_yC(=O)NR^1R^2$, $-(CH_2)_yNHC(=O)R^2$, $-(CH_2)_yNR^1R^2$, $-(CH_2)_yOR^2$, $-(CH_2)_ySR^2$, $-(CH_2)_y$ heterocyclyl, $-(CH_2)_y$ aryl, $-(CH_2)_y$ heteroaryl, $-NH$ -aryl, $-NH$ -heteroaryl, NH -heterocyclyl and $-(CH_2)_mP(=O)(alkyl)_2$; in which y and m are independently selected from 0, 1, 2, 3 and 4 and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

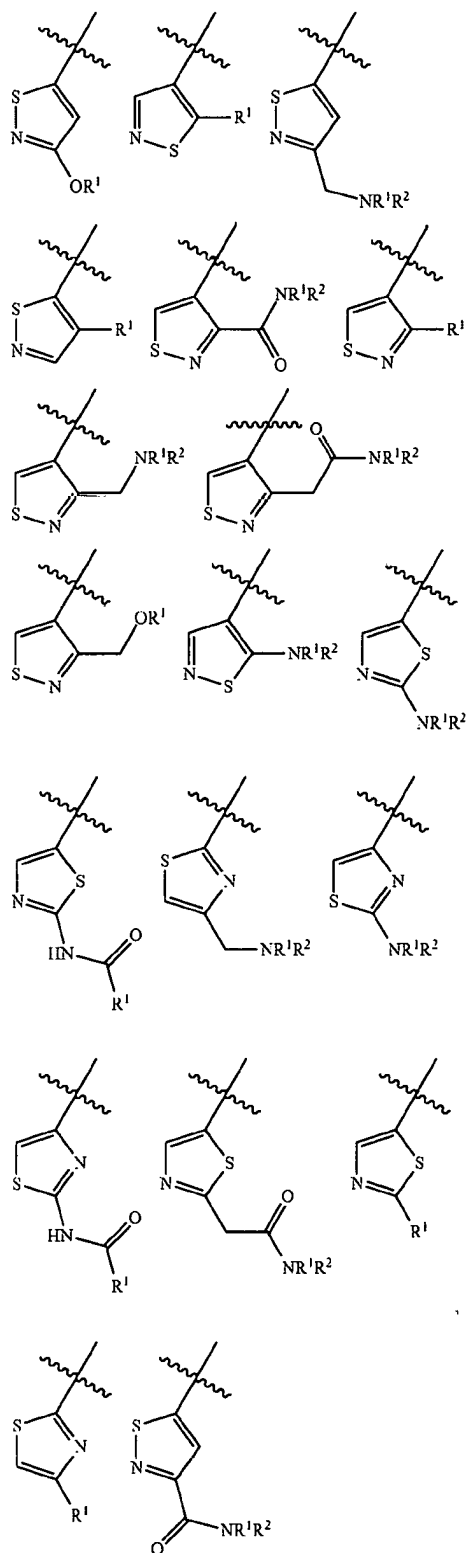
Non-limiting examples of this class include compounds of formula VI in which Ring E is:



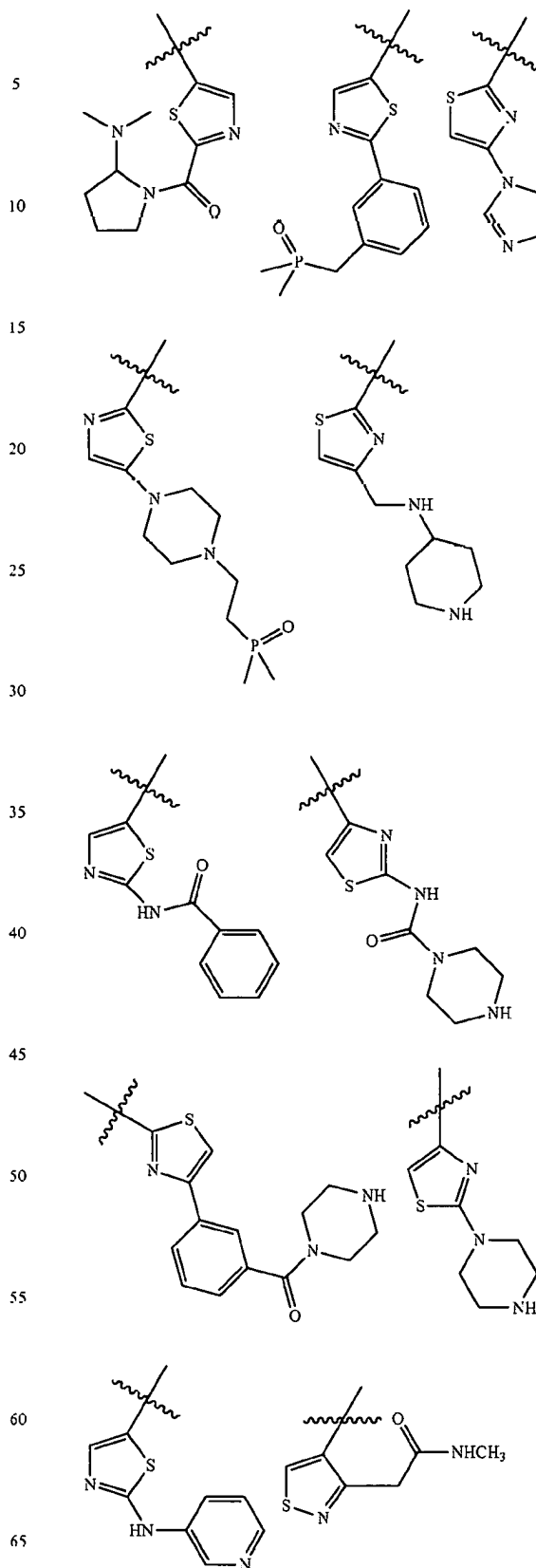
In another specific embodiment, Ring E is a 5-membered heteroaryl comprising carbon atoms and 1-3 heteroatoms selected from N and S.

45

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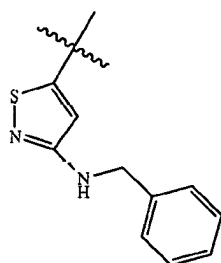
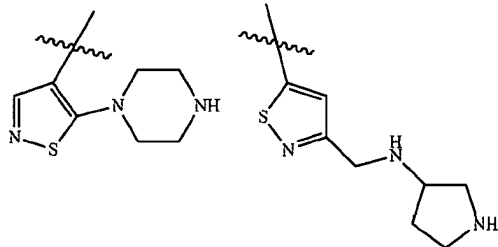
46



Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:

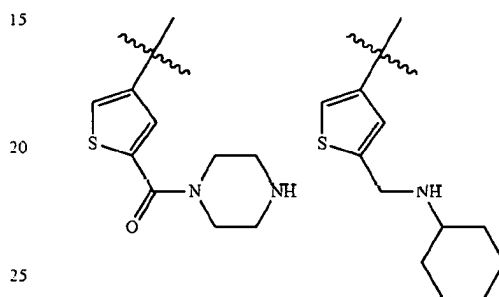
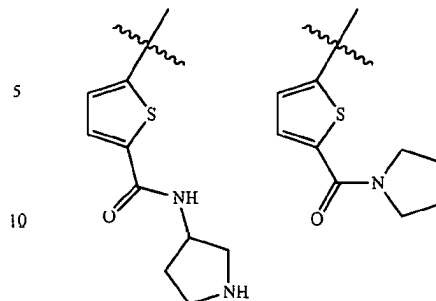
47

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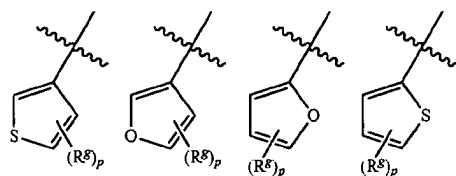


48

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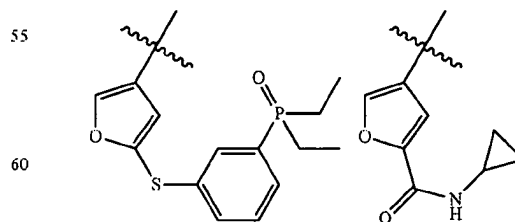
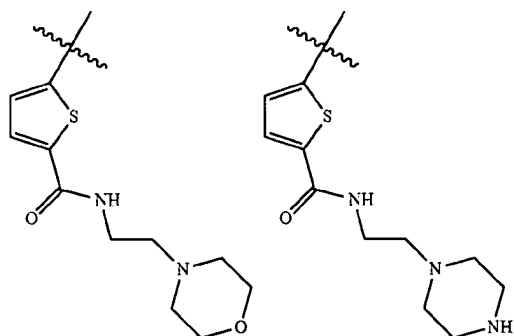
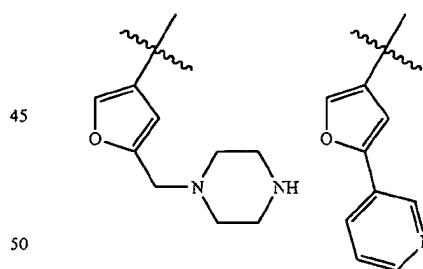
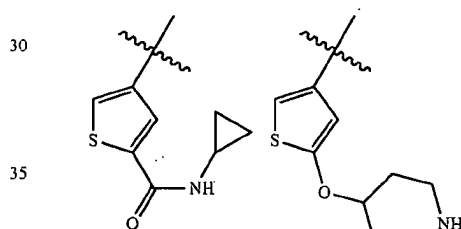


Other non-limiting examples include compounds of formula VI in which Ring E is furan or thiofuran:



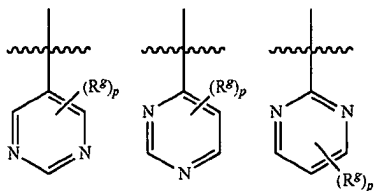
in which p is defined previously and the total number of substituents R^E does not exceed the normal available valencies.

Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:



In another embodiment, Ring E is a 6-membered heteroaryl ring. For example, Ring E can be a pyrimidine of the following types:

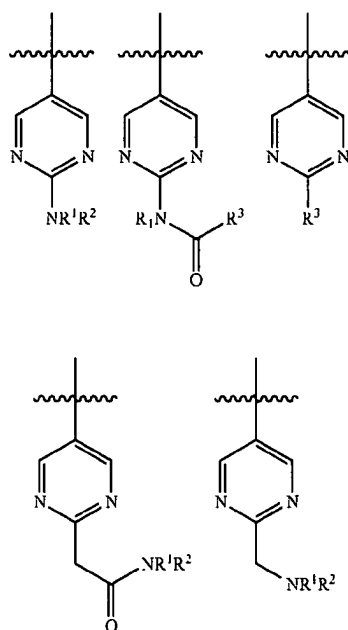
49



in which p is as previously described and the total number of substituents R^g does not exceed the normal available valencies.

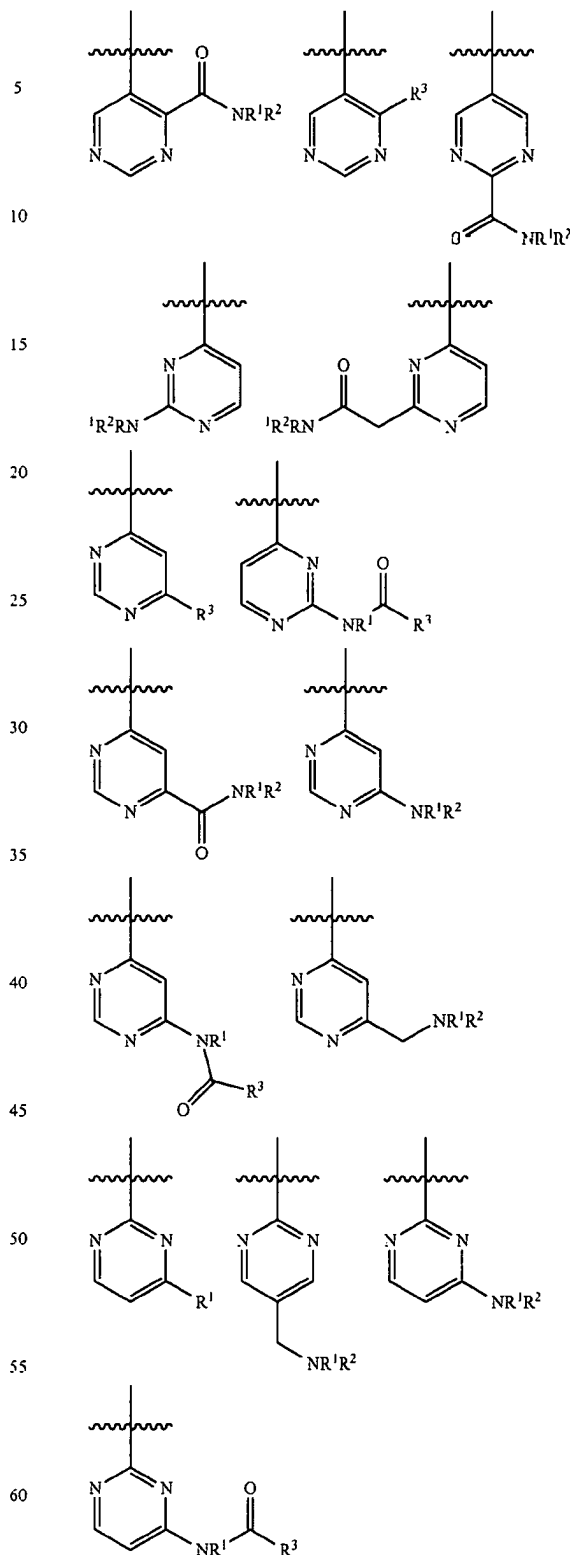
Of particular interest is a class of compounds as described above in which R^g is selected from the group consisting of $-R^1$, $-P(=O)(R^3)_2$, $-OR^2$, $-NR^1R^2$, $-C(O)YR^2$, $-NR^1C(O)YR^2$, $-NR^1SO_2R^2$, $-S(O)_yR^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$. In another subclass of interest, are compounds of the above embodiment in which R^g is $NHC(O)R^1$, $NHC(O)NHR^1$, $C(O)NHR^1$, $C(O)NR^1R^2$, NR^1R^2 , an aryl, heteroaryl, substituted alkyl or heterocyclyl. Non limiting examples of R^a are $-OCH_2CH_2NR^1R^2$, $-OCH_2C(O)NR^1R^2$, $-NR^1C(O)NR^1R^2$, $-(CH_2)_yC(O)NR^1R^2$, $-(CH_2)_yNHC(=O)R^2$, $-(CH_2)_yNR^1R^2$, $-(CH_2)_yOR^2$, $SO_2NR^1R^2$, $-(CH_2)_ySR^2$, $-(CH_2)_y$ heterocyclyl, $-(CH_2)_y$ aryl, $-(CH_2)_y$ heteroaryl, NH-aryl, NH-heteroaryl, NH-heterocyclyl and $-(CH_2)_mP(=O)(alkyl)_2$; in which y and m are independently selected from 0, 1, 2, 3 and 4 and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

Non-limiting examples of this class are compounds of formula VI in which Ring E is:



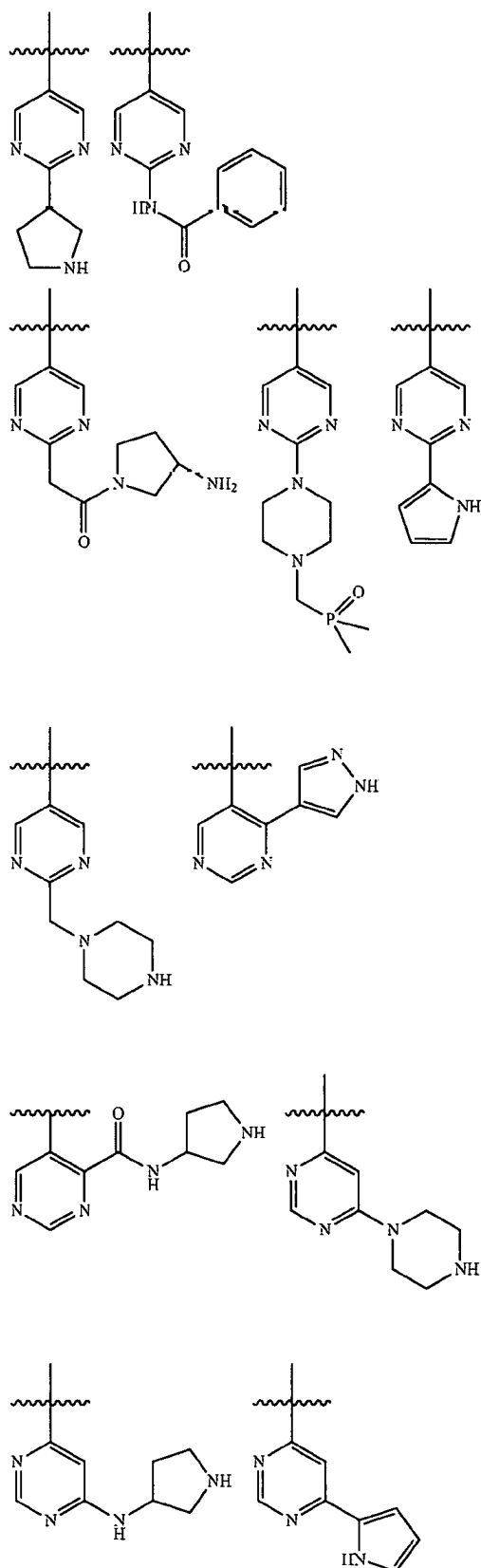
50

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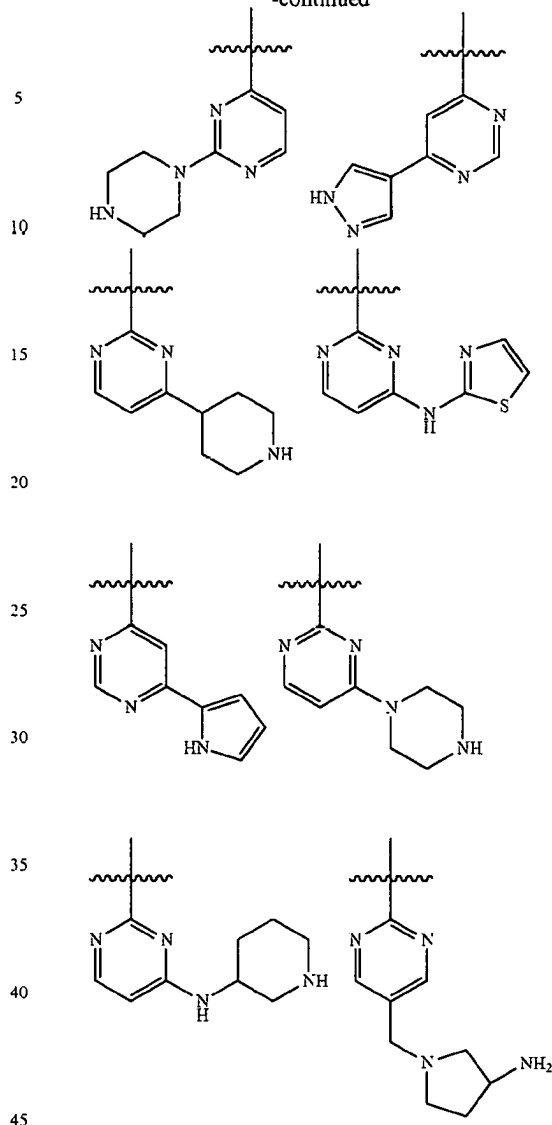
Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:

51



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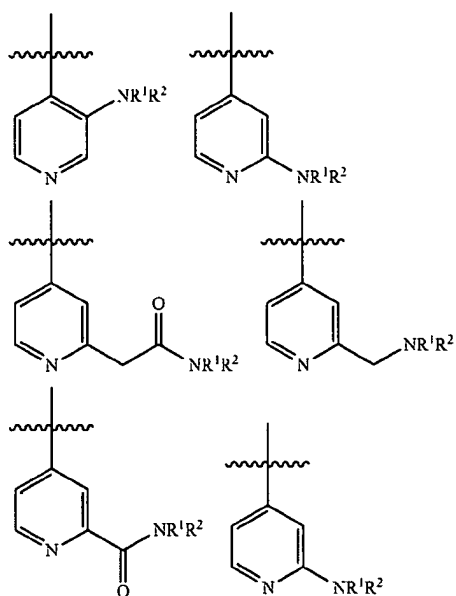
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In another embodiment, Ring E is a pyridine substituted with 1-4 R^g . Of particular interest is a class of compounds as described above in which R^g is selected from the group consisting of $-R^1$, $-P(=O)(R^3)_2$, $-OR^2$, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1SO_2R^2$. In another subclass of interest, are compounds of the above embodiment in which R^g is $NHC(O)R^2$, NR^1R^2 , an aryl, heteroaryl, substituted alkyl or heterocyclyl. Non limiting examples of R^g are $-(CH_2)_yC(=O)NR^1R^2$, $-(CH_2)_yC(=O)aryl$, $-(CH_2)_yC(=O)heteroaryl$, $-(CH_2)_yC(=O)heterocyclyl$, $-(CH_2)_yNHC(=O)R^2$, $-(CH_2)_yNR^1R^2$, $-(CH_2)_yOR^2$, $-(CH_2)_ySR^2$, $-(CH_2)_yheterocyclyl$, $-(CH_2)_yaryl$, $-(CH_2)_yheteroaryl$, $-NH-aryl$, $NH-heteroaryl$, $NH-heterocyclyl$ and $-(CH_2)_mP(=O)(alkyl)_2$, in which y and m are independently selected from 0, 1, 2, 3 and 4; and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

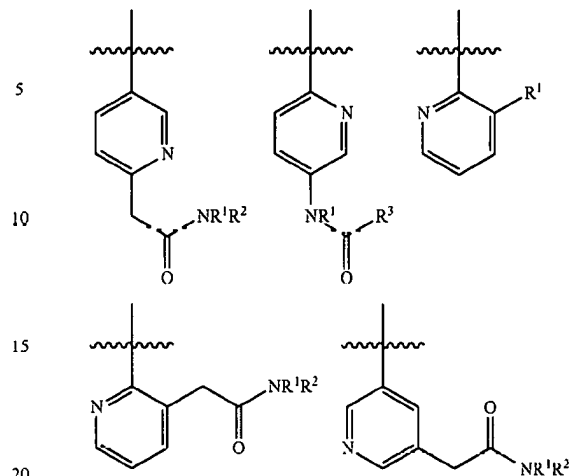
Non-limiting examples of this class are compounds of formula VI in which Ring E is:

53

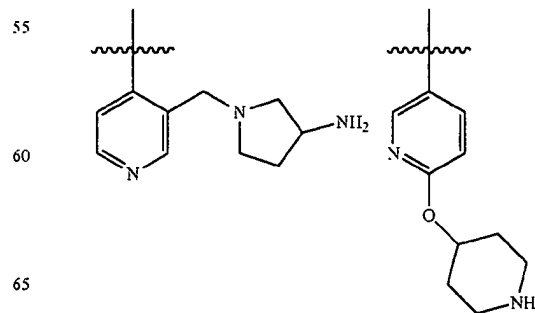
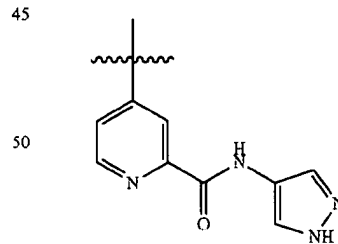
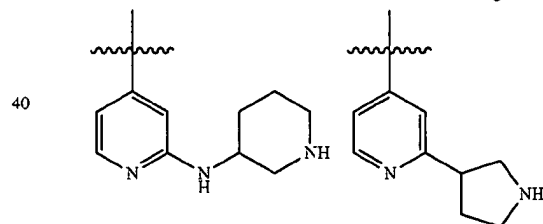
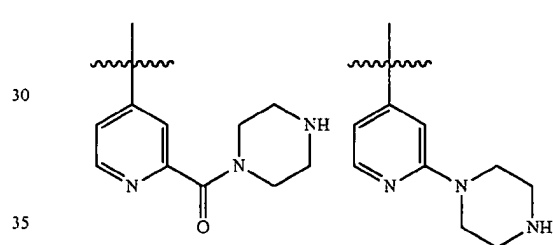
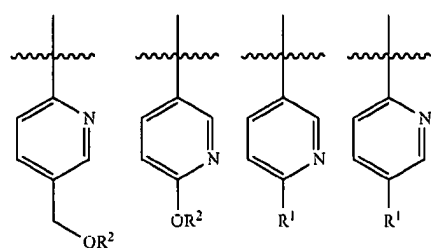
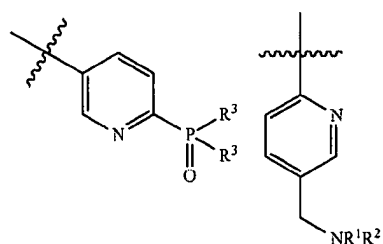
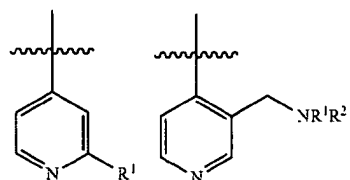
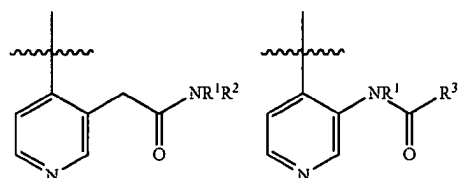


54

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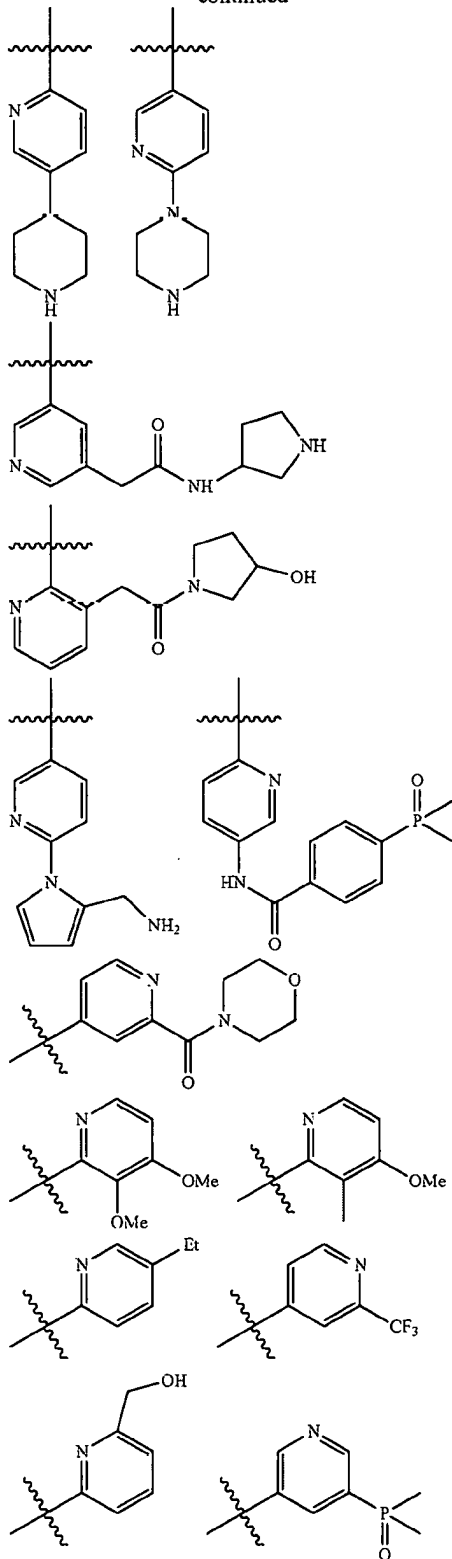


Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:



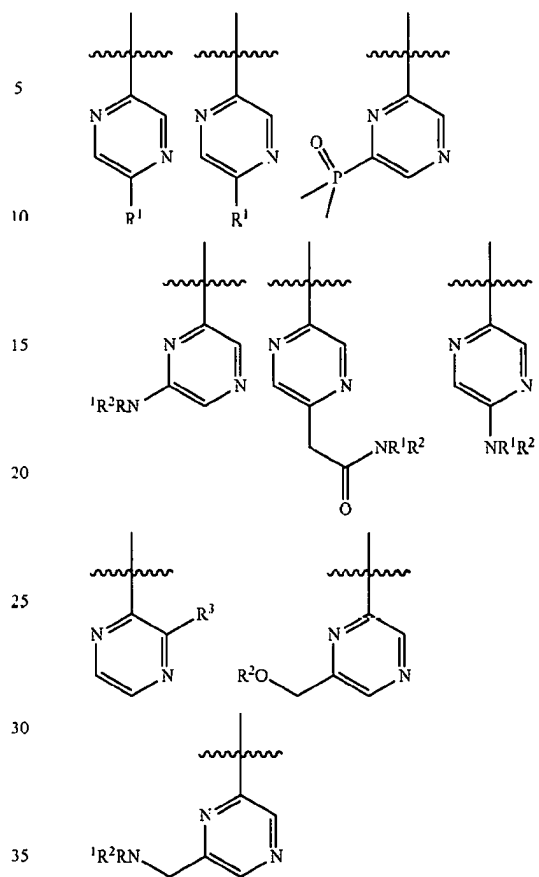
55

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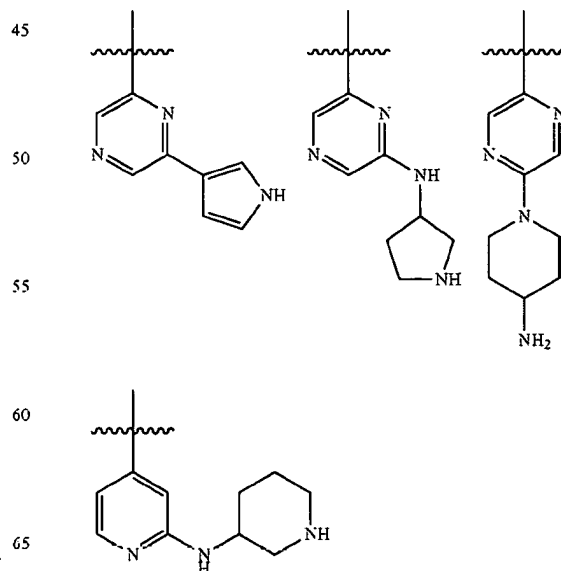


In another embodiment, Ring E is a pyrazine substituted with 1-3 R⁸ groups. Non-limiting examples of this class of compounds in which Ring E is:

56

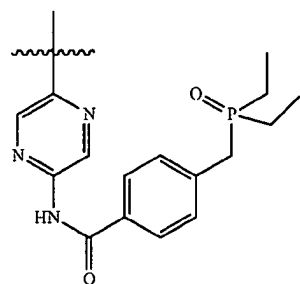
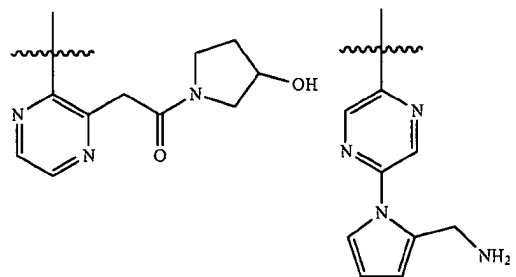
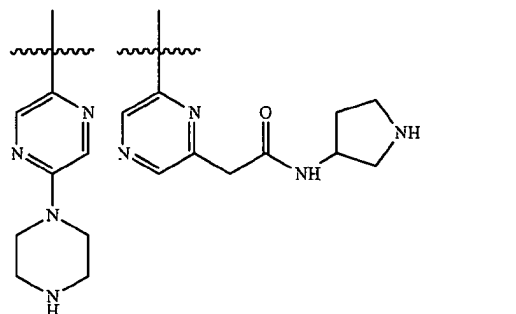
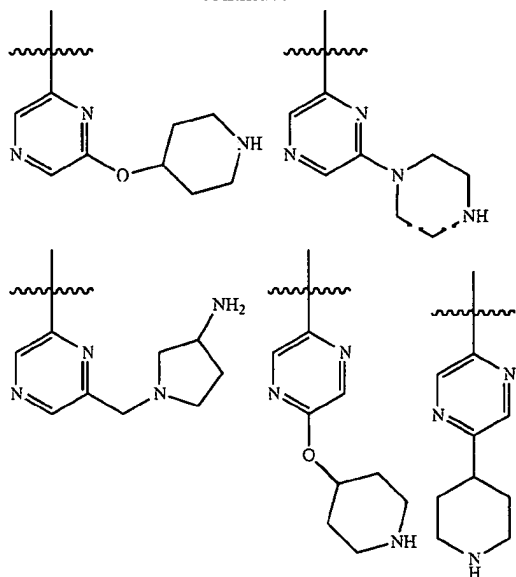


Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:



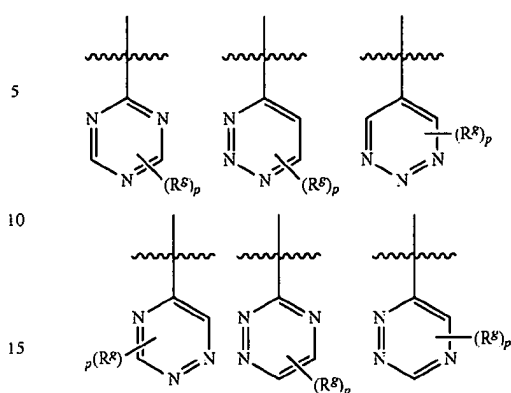
57

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In another embodiment, Ring E is a triazine substituted with 1 to 2 R^8 groups. Examples include compounds in which Ring E has the following formulae:

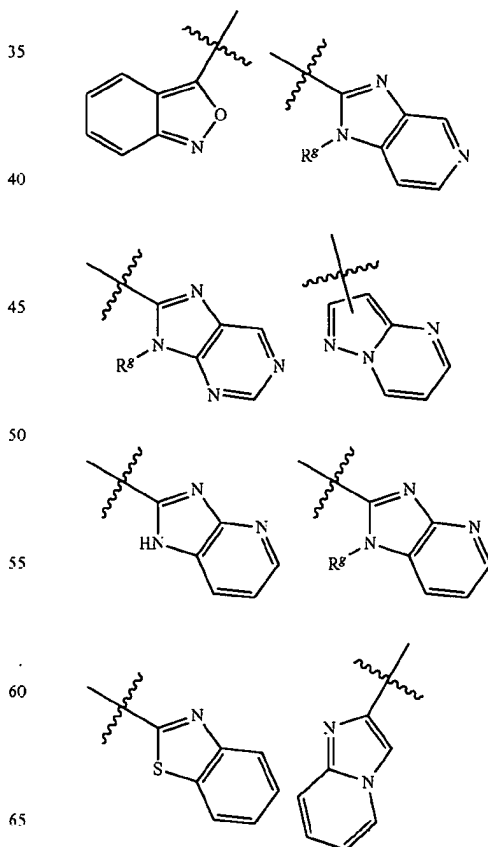
58



in which p is defined previously and the number of substituents R^8 does not exceed the maximum available valencies, which in the triazine case p is 0, 1 or 2.

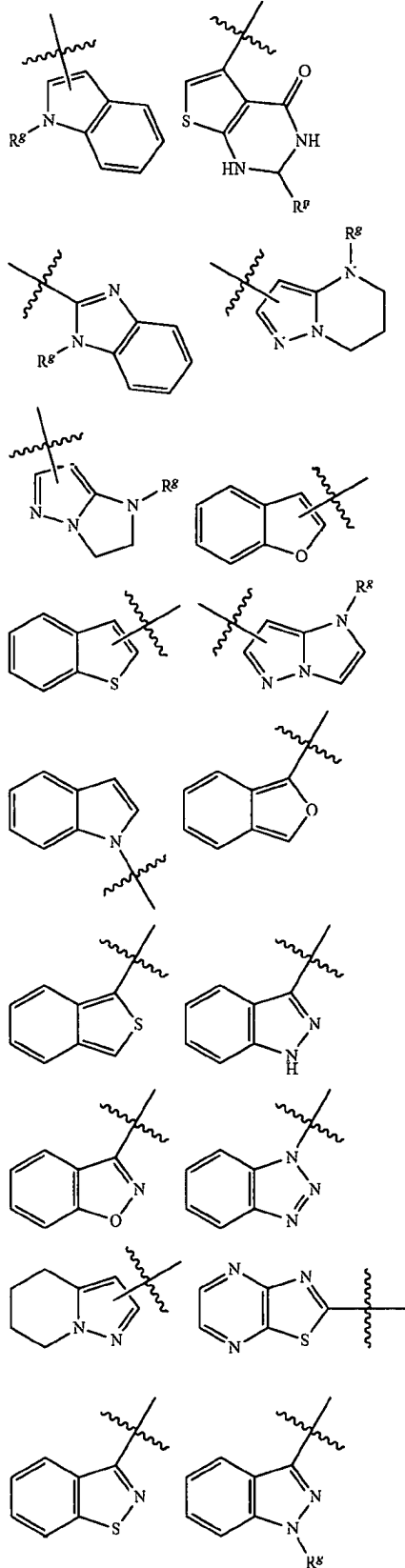
In one embodiment, Ring E is an aryl, a carbocyclyl or a 5-, 6- or 7-membered heterocyclic or heteroaryl ring which is fused with a 5- or 6- or 7-membered saturated, partially saturated or unsaturated ring, and Ring E is optionally substituted with 1-5 R^8 groups.

In certain embodiments, Ring E is a 5,6- or 5,5-bicyclic fused system. Non-limiting examples include compounds of formula VI in which Ring E has the following formulae:



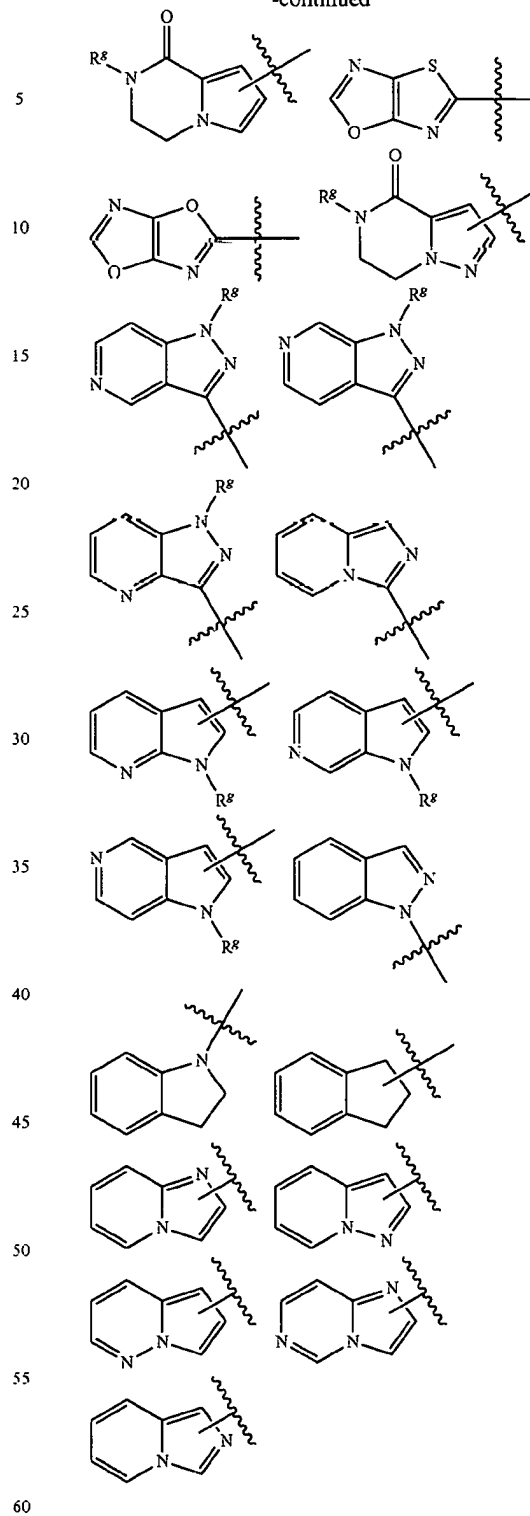
59

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60

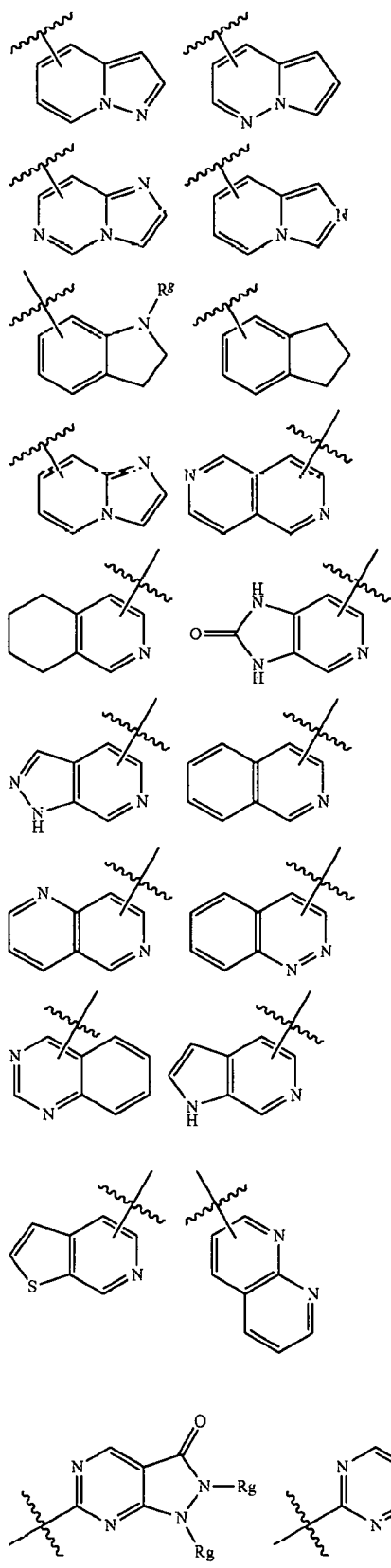
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and the depicted fused ring systems can be substituted with additional R^g groups.

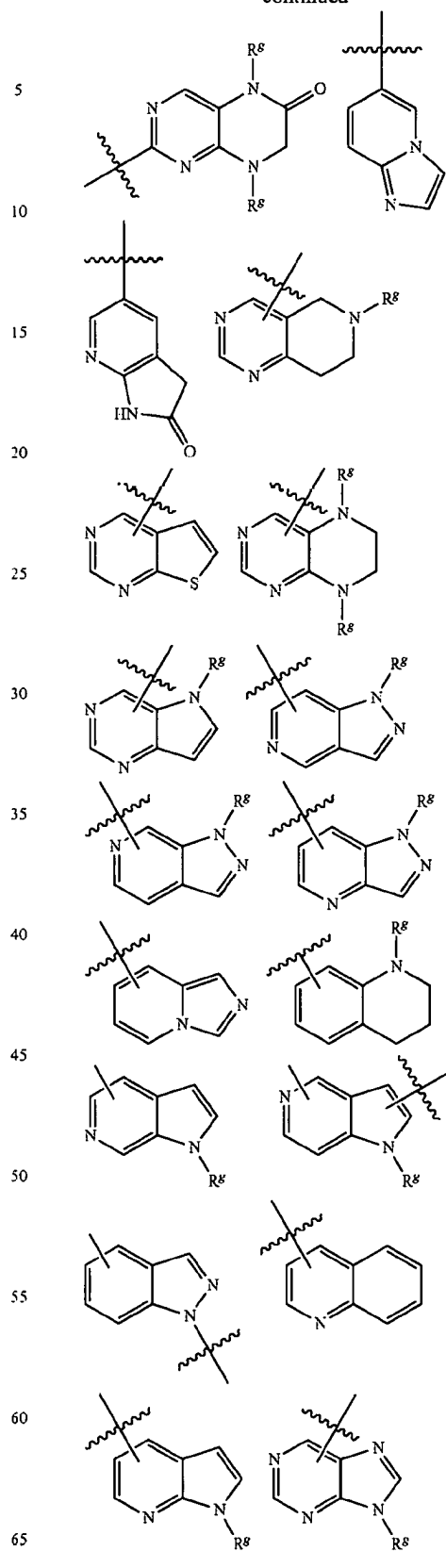
In some other embodiments of interest, Ring E is a 6,6- or 6,5-bicyclic fused system. Non limiting examples of this class include compounds of formula VI in which Ring E has the following formulae:

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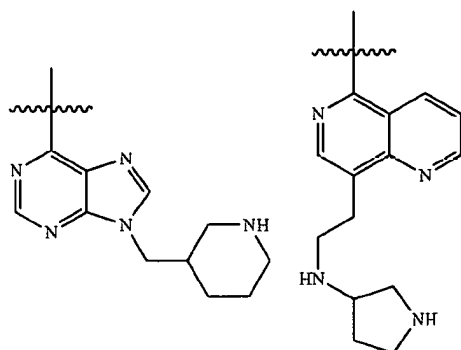
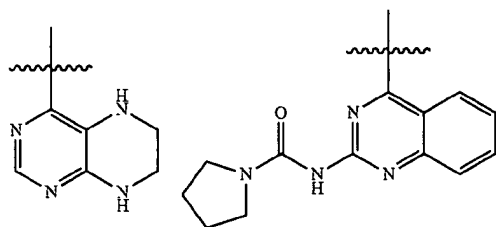
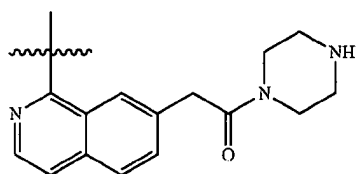
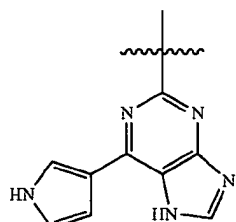
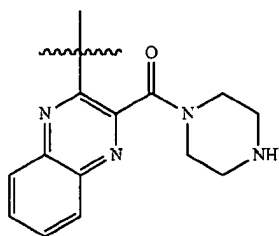
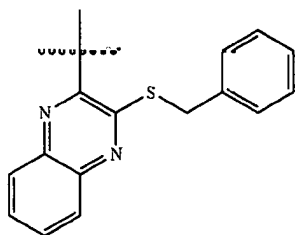
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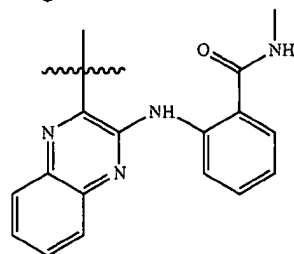
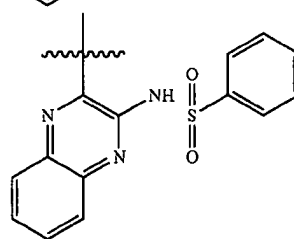
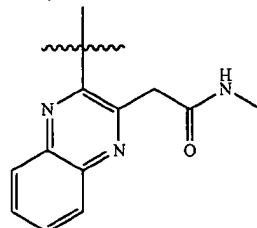
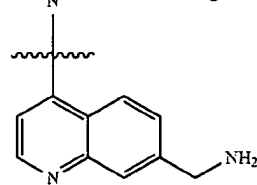
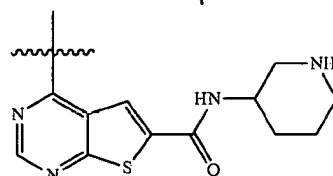
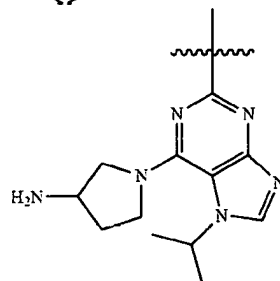
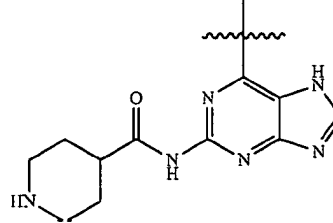
and the depicted fused ring systems can be substituted with additional R⁸ groups.

Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:



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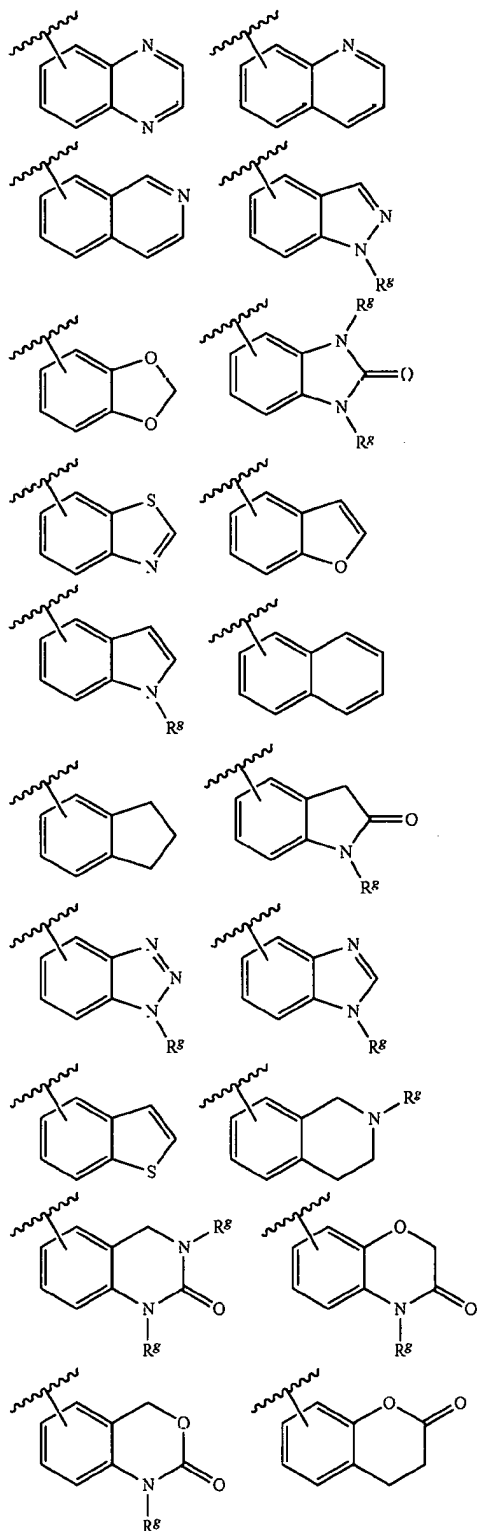
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In some other embodiments of interest, Ring E is an aryl fused with a 5-, 6- or 7-membered saturated, partially satu-

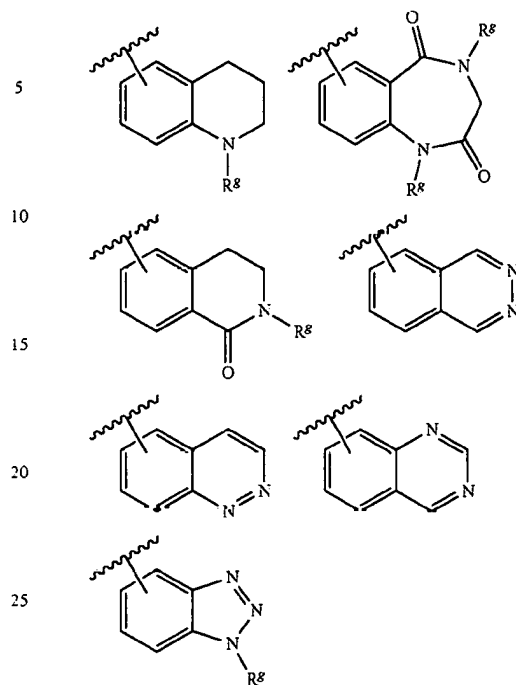
65

rated or unsaturated ring, and Ring E is substituted with 1-5 R^g groups. Non limiting examples of this class include compounds of formula VI in which Ring E has the following formulae:

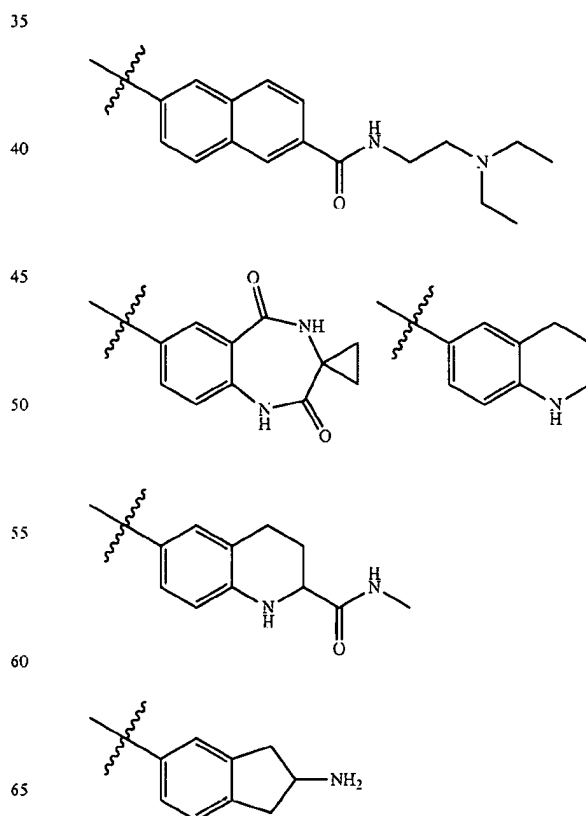


66

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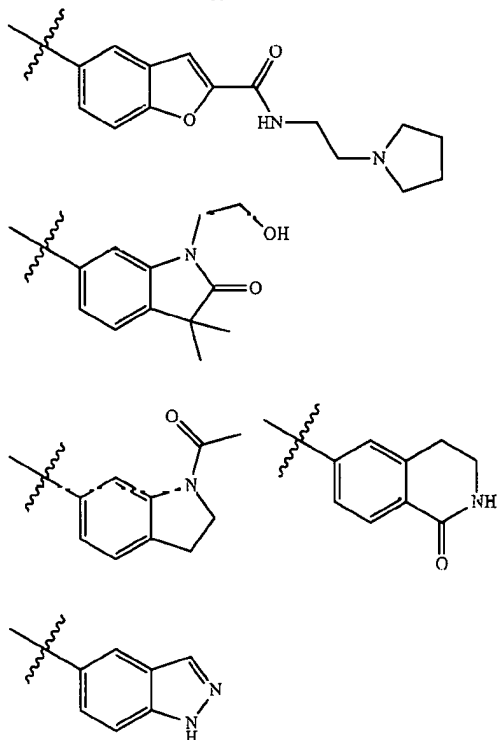


Specific, non-limiting illustrative examples of this class include compounds of formula VI in which substituted Ring E is of the following formulae:



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In embodiments of the compounds of formula VI, Ring A is a 6-membered ring heteroaryl. Examples of this class are compounds of the above classes and subclasses in which Ring A is a pyridine, pyrazine, pyridazine, pyrimidine or triazine.

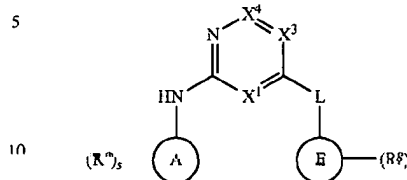
In still other embodiments, Ring A is a 5-membered ring heteroaryl. Examples of this class are compounds of the above classes and subclasses in which Ring A is imidazole, pyrazole, tetrazole, oxazole, thiazole, isoxazole, pyrrole, and the like.

Of particular interest is a class of compounds as described above in which R^a is selected from the group consisting of halo, $-P(=O)(R^3)_2$, $-R^1$, $-OR^2$, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)NR^2$, $-C(O)NR^1R^2$, $C(O)OR^1$, $-SO_2NR^1R^2$, $-SO_2R^1$, SO_2R^2 . In another subclass of interest, are compounds of the above embodiment in which R^a is $-P(=O)(alkyl)_2$, alkyl, alkynyl, halo, aryl, heteroaryl, heterocyclyl, O-alkyl (i.e. OMe and the like), $-CN$, $-C(O)NH$ -alkyl, $-C(O)NH$ -heterocyclyl, OH, $-NR^1R^2$, $NHS(O)_2$ -alkyl, $NHS(O)_2$ -aryl. Non limiting examples of R^a are is $-(CH_2)_mP(=O)(Me)_2$, $-(CH_2)_mP(=O)(Et)_2$, F, Cl, CF_3 , OCF_3 , $-(CH_2)_yC(=O)NR^1R^2$, $-(CH_2)_yC(=O)aryl$, $-SO_2NR^1R^2$, $NHSO_2R^1$, lower alkyl, $-(CH_2)_yC(=O)heteroaryl$, $-(CH_2)_yC(=O)heterocyclyl$, $-(CH_2)_yNHC(=O)R^2$, $-(CH_2)_yNR^1R^2$, $-(CH_2)_yOR^2$, $-(CH_2)_ySR^2$, $-(CH_2)_yheterocyclyl$, $-(CH_2)_yaryl$, $-(CH_2)_yheteroaryl$, NH-aryl, NH-heteroaryl, NH-heterocyclyl, in which y and m are independently selected from 0, 1, 2, 3 and 4; and alkyl include straight (i.e. unbranched or acyclic), branched and cyclic alkyl groups and alkyl, aryl, heteroaryl, heterocyclyl groups are optionally substituted.

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The invention also features compounds of Formula VIa:

Formula VIa



wherein

X^1 is NR^{b1} or CR^{b1} ;

X^2 is NR^{d1} or CR^{d1} ;

X^3 is NR^{e1} or CR^{e1} ;

Ring A and Ring E are each an independently selected aryl or heteroaryl ring, the heteroaryl ring being a 5- or 6-membered ring containing 1 to 4 heteroatoms selected from N, O and S(O);

each occurrence of R^a , R^b , R^d , R^e , and R^f is independently selected from the group consisting of halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(N-NR^1R^2)YR^2$, $-YP(O)(YR^3)(YR^3)$, $-Si(R^{3a})_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; or alternatively, each R^a and R^f may also be or include an independently selected moiety, $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member;

R^{b1} , R^{d1} and R^{e1} are absent;

or alternatively two adjacent substituents selected from R^d , R^{d1} , R^e , and R^{e1} or two adjacent R^a moieties, can form, with the atoms to which they are attached, a fused, 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4 heteroatoms selected from N, O and S(O), and which may bear up to four substituents suitable for heterocycles (see *infra*), a variety of which are illustrated in exemplary compounds disclosed herein; at least one of R^a and R^f is or contains a moiety, $-P(=O)(R^3)_2$ or a ring system containing the moiety $-P(=O)(R^3)-$ as a ring member;

L is O or NH;

r is 0, 1 or 2;

s is 1, 2, 3, 4 or 5;

p is 1, 2, 3 or 4;

each occurrence of Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$;

each occurrence of R^1 and R^2 is independently H or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl moiety;

each occurrence of R^3 is independently an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl moiety, or two adjacent R^3 moieties combine to form a ring system including a phosphorus atom;

each occurrence of R^{3a} is independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic, and heteroaryl;

alternatively, each NR^1R^2 moiety may be a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which can be optionally substituted and which contains 0-2 additional heteroatoms selected from N, O and S(O); and

each of the foregoing alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocyclic moieties is optionally substituted.

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In certain embodiments of the compounds of Formula VIA are further defined as follows (1) X^1 is N; (2) X^3 is N and X^4 is CR^e ; (3) X^3 is CR^d and X^4 is CR^e ; (4) X^1 is CR^b ; (5) X^3 is N and X^4 is CR^e ; or (6) X^3 is CR^d and X^4 is CR^e .

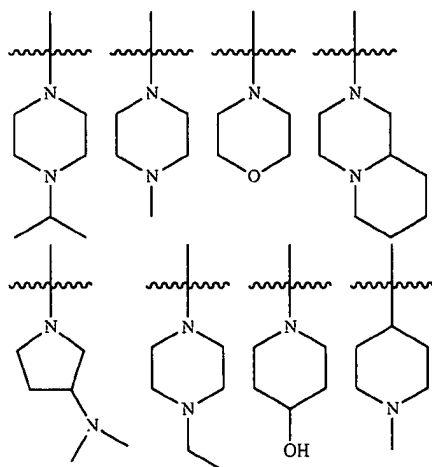
In certain specific embodiments of the compounds of Formula VIA, when X^3 is CR^d , R^d is selected from Cl, F, C1-C4 alkyl, trihaloalkyl, cycloalkyl, C2-C4 alkenyl, and alkynyl. In such embodiments, Cl, F, Me and cyclopropyl are of particular interest.

In another embodiment of the compounds of Formula VIA, X^3 is CR^d and X^4 is CR^e wherein R^d and R^e , together with the atoms to which they are attached, form a fused, 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4 heteroatoms selected from N, O and S(O), and which may bear up to four substituents.

Compounds of Formula VIA of particular interest, generally and including the individual embodiments described above, include those in which s is 1, 2, 3 or 4, and each of the substituents R^a is independently selected from halo, $-R^1$, $-OR^1$, $-NR^1R^2$ and $-P(=O)(R^1)_2$, wherein each R^1 and R^2 moiety may be further substituted or unsubstituted. In certain embodiments, the compounds include at least one substituent R^a that is $-OR^2$ and R^2 is selected from C1-C6 alkyl, C2-C6, and C2-C6 alkynyl. In such cases, as illustrated in compounds shown herein, MeO—, EtO— and iPrO— are often chosen as an W moiety.

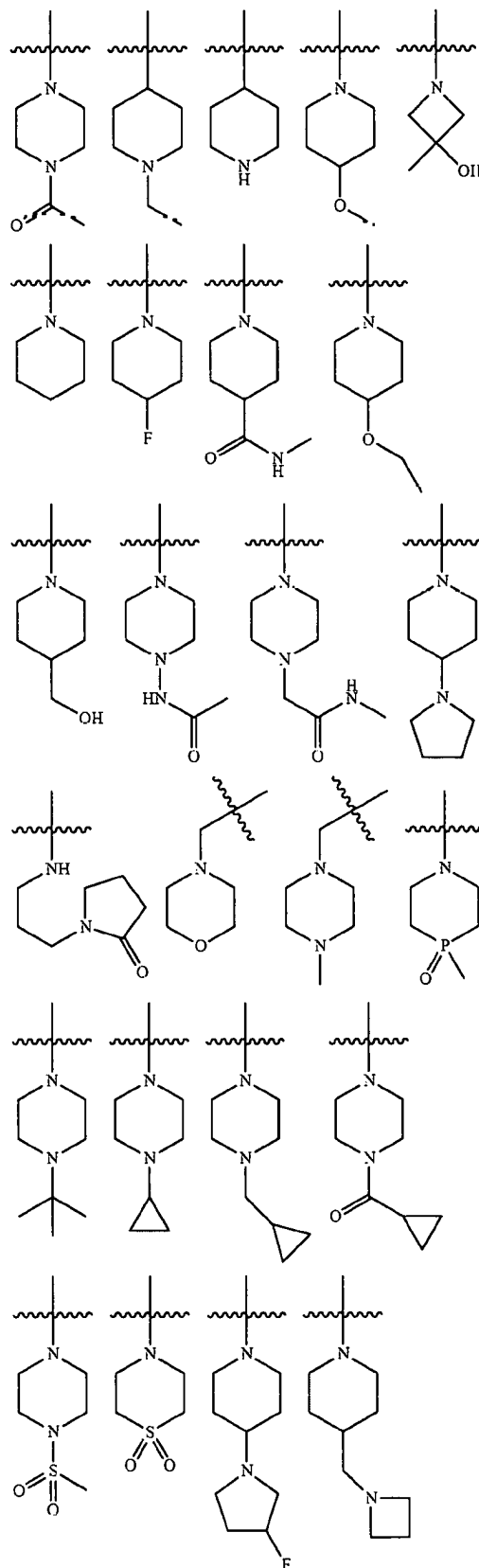
Compounds of Formula VIA, generally and including the individual embodiments described thus far, also include compounds having at least one substituent R^a which is a 4-, 5-, 6- or 7-membered heterocyclic or 5- or 6-membered heteroaryl moiety, linked to Ring A either directly or by an ether bond, and which may be further substituted with 1-3 substituents independently selected from halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-$, $-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^3)_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$, wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$.

For example, compounds of Formula VIA include those having a heterocyclic or heteroaryl substituent R^a is selected from the following:



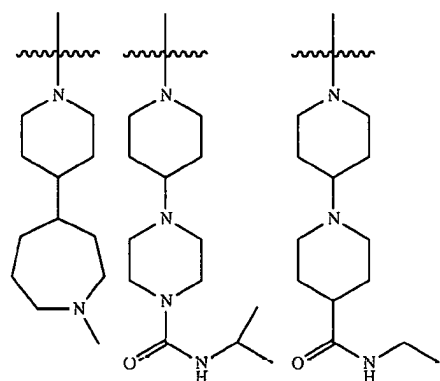
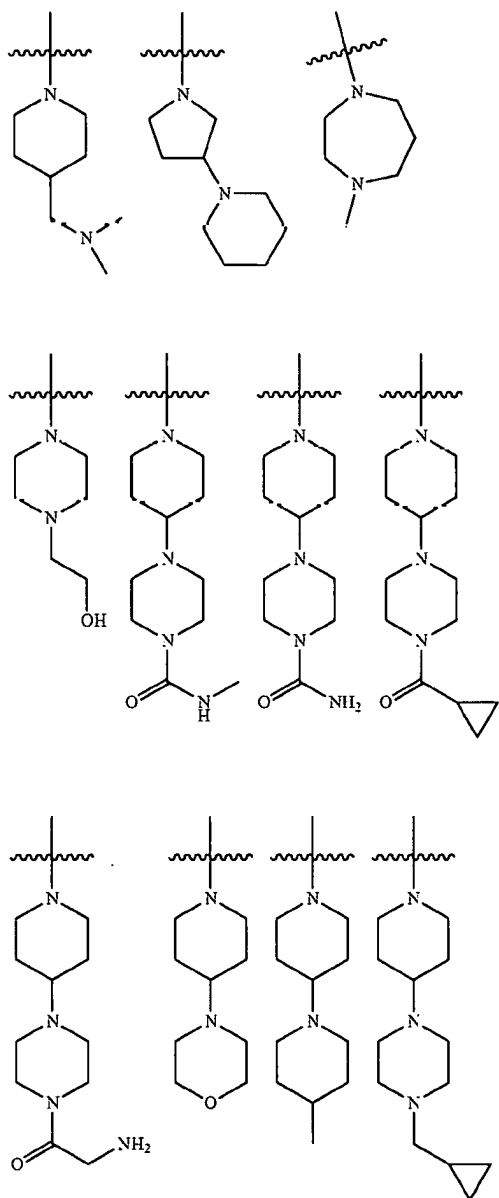
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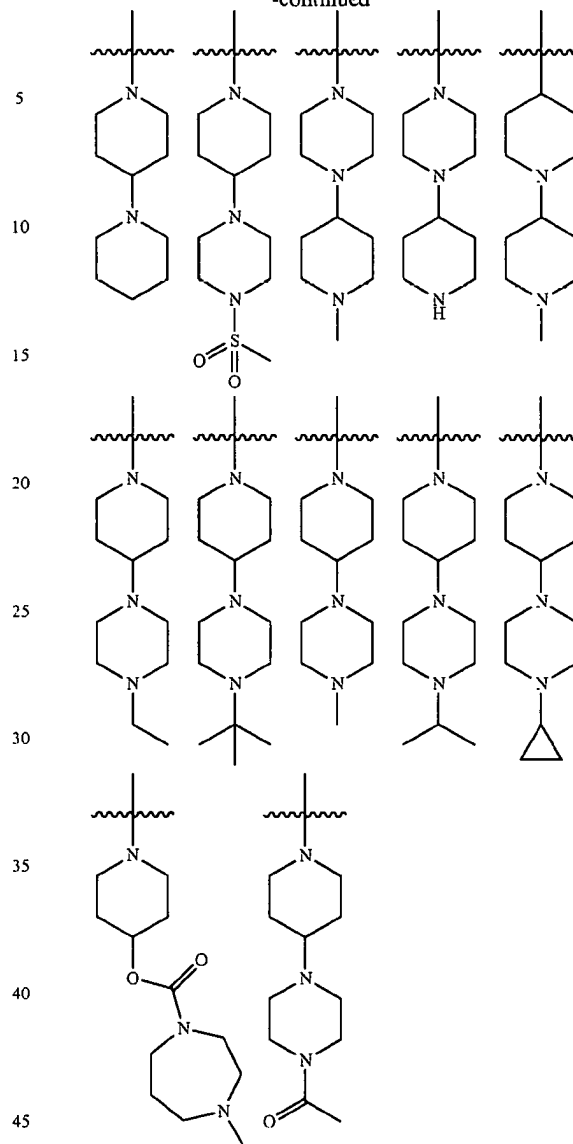
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Compounds of Formula VIA, generally and, again, including the individual embodiments described thus far, also include compounds of Formula VIA in which at least one substituent R^a is or bears a moiety, $-P(=O)(R^3)_2$, in which R^3 is a C1-C4 alkyl.

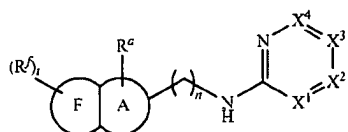
Compounds of Formula VIA, generally and, again, including the embodiments described thus far, also include embodiments of Formula VIA in which L is NH, Ring E is aryl, and each R^g is independently selected from halo, $-R^1$, $-OR^2$, $-S(O)_2R^2$ and $-P(=O)(R^3)_2$. In certain embodiments, Ring E contains at least one such R^g moiety in the ortho position relative to the ring atom attached to L. In other embodiments, that R^g moiety is in the meta position relative to the ring atom attached to L, and in still other embodiments, that R^g moiety is in the para position relative to the ring atom attached to L.

Embodiment of the compounds of formulas VI and VIA, generally and, again, including the individual embodiments

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described thus far, also include those compounds in which the group $P(=O)(R^3)_2$ is selected from $P(=O)(CH_3)_2$ and $P(=O)(CH_2CH_3)_2$.

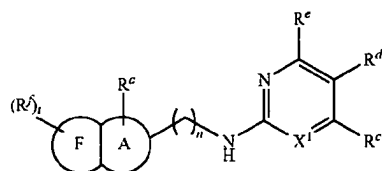
In another embodiment of compounds of Formula I, two adjacent R^a form a 5-, 6- or 7-membered saturated, partially saturated or unsaturated Ring F which is substituted with 1-4 R' groups. This class of compounds is represented by compounds of formula VII:



Formula VII

in which Ring A, R^a , R' , n , X^1 , X^2 , X^3 and X^4 are as defined in Formula I, t is 1, 2, 3 or 4; and Ring F is an aryl, a carbocyclyl, a 5- or 6- or 7-membered heteroaryl or heterocyclyl ring substituted with 1-4 R' groups.

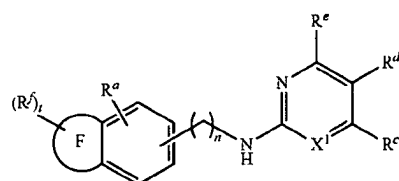
One class of compounds which is of special interest for use in the invention are compounds of Formula VII are those in which X^2 is CR^c , X^3 is CR^d and X^4 is CR^e . This class is illustrated by compounds of formula VIIA:



Formula VIIA

in which Ring A, Ring F, R^a , R' , t , n , X^1 , R^c , R^d and R^e are as defined previously in Formula VII.

One class of compounds of further interest are compounds of Formula VIIA in which Ring A is a phenyl. This is represented by compounds of Formula VIIB:

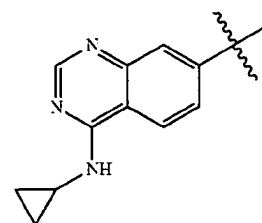
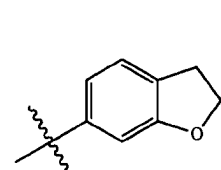
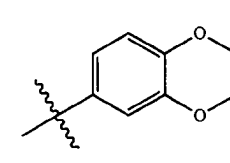
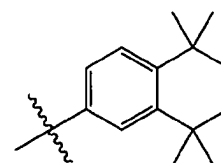
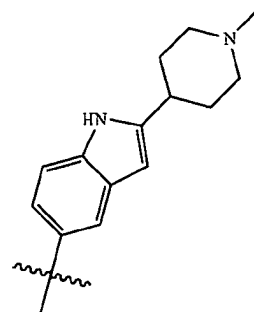
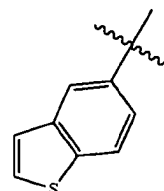
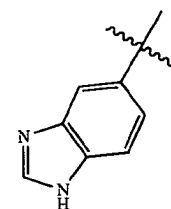
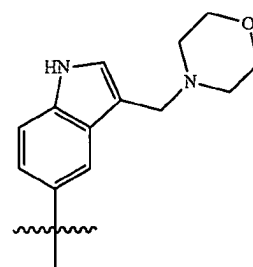
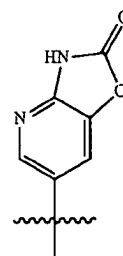
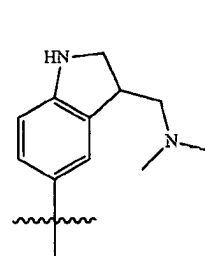
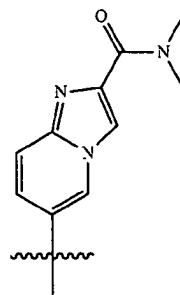
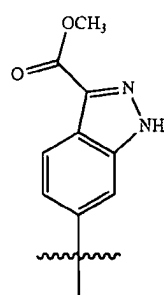


Formula VIIB

in which Ring F, R^a , R' , t , n , X^1 , R^c , R^d and R^e are as described in Formula VII.

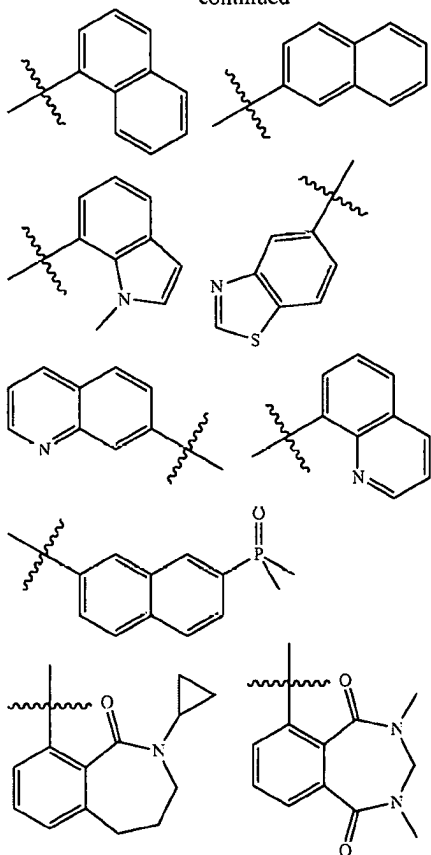
In Formulas VII, VIIA, and VIIB, Ring A and Ring F together form a fused ring system. Fused ring systems that can be utilized in compounds of formulas VII, VIIA, and VIIB include, without limitation, those depicted for Ring E of Formula VI (see below) and the following fused ring systems:

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The fused ring systems are optionally substituted with additional R^a or R^f groups. Of special interest are compounds of formula VII or VIIA or VIIB in which R^f is or contains

$P(=O)(R^3)_2$. Examples of R^f containing $P(=O)(R^3)_2$ include, without limitation, $-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-P(=O)(R^3)_2$, $-(CH_2)_m-O-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-C(O)O-(CH_2)_m-P(=O)(R^3)_2$, and $-(CH_2)_m-C(O)NR^1-(CH_2)_m-P(=O)(R^3)_2$, in which m is 0, 1, 2, 3 or 4 and ring systems containing the moiety $P(=O)(R^3)_2$ as a ring member.

Of other special interest are compounds of Formula VII or VIIA or VIIB in which R^o is or contains $-P(=O)(R^3)_2$.

In one embodiment of any of the above classes and subclasses of compounds, Ring A is a phenyl group substituted with 1-5 R^a moieties. In certain embodiments of any of the above classes and subclasses of compounds, Ring A is a 6-membered ring heteroaryl (e.g., a pyridine, pyrazine, pyridazine, pyrimidine or triazine ring). In still other embodiments of any of the above classes and subclasses of compounds, Ring A is a 5-membered ring heteroaryl (e.g., an imidazole, pyrazole, tetrazole, oxazole, thiazole, isoxazole, or pyrrole ring).

In another embodiment of any of the above classes and subclasses of compounds, R^a is selected from halo, $P=O$ (R^3)₂, $-R^1$, $-OR^2$, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)NR^2$, $-C(O)NR^1R^2$, $-C(O)OR^1$, $-SO_2NR^1R^2$, $-SO_2R^1$, and $-NR^1SO_2R^2$.

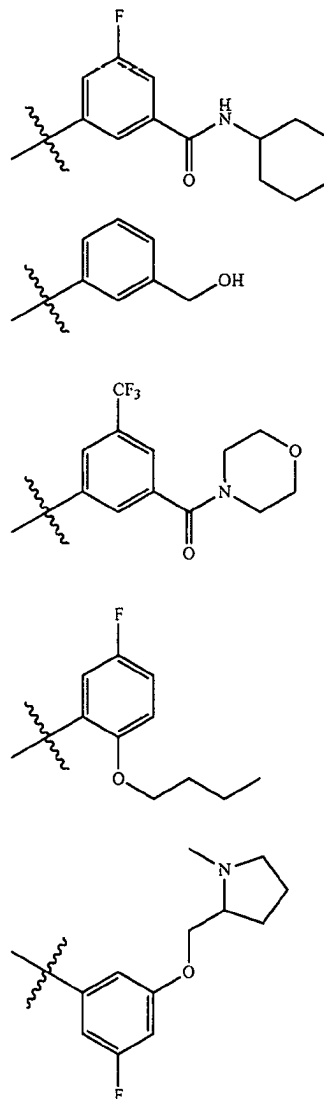
Another subclass of interest are compounds of the above 65 embodiment in which R² is —P(=O)(alkyl)₂, alkyl, alkynyl, halo, aryl, heteroaryl, heterocyclyl, —O-alkyl (i.e. OME and

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the like), $-\text{CN}$, $-\text{C(O)NH-alkyl}$, $-\text{C(O)NH-aryl}$, $-\text{C(O)NH-heterocyclyl}$, OH , NR^1R^2 , $\text{NHS(O)}_2\text{-alkyl}$, $\text{NHS(O)}_2\text{-aryl}$. Non limiting examples of R^a include $-(\text{CH}_2)_m\text{P(=O)(Me)}_2$, $-(\text{CH}_2)_n\text{-P(=O)(Et)}_2$, $-\text{F}$, $-\text{Cl}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-(\text{CH}_2)_j\text{C(=O)NR}^1\text{R}^2$, $-(\text{CH}_2)_j\text{C(=O)aryl}$, $-\text{SO}_2\text{NR}^1\text{R}^2$, $-\text{NiSO}_2\text{R}^1$, lower alkyl, $-(\text{CH}_2)_j\text{C(=O)heteroaryl}$, $-(\text{CH}_2)_j\text{C(=O)heterocyclyl}$, $-(\text{CH}_2)_j\text{NHC(-O)R}^2$, $-(\text{CH}_2)_j\text{NR}^1\text{R}^2$, $-(\text{CH}_2)_j\text{OR}^2$, $-(\text{CH}_2)_j\text{SR}^2$, $-(\text{CH}_2)_j\text{heterocyclyl}$, $-(\text{CH}_2)_j\text{aryl}$, $-(\text{CH}_2)_j\text{heteroaryl}$, $-\text{NH-aryl}$, $-\text{NH-heteroaryl}$, $-\text{NH-heterocyclyl}$, wherein y and m are independently selected from 0, 1, 2, 3 and 4.

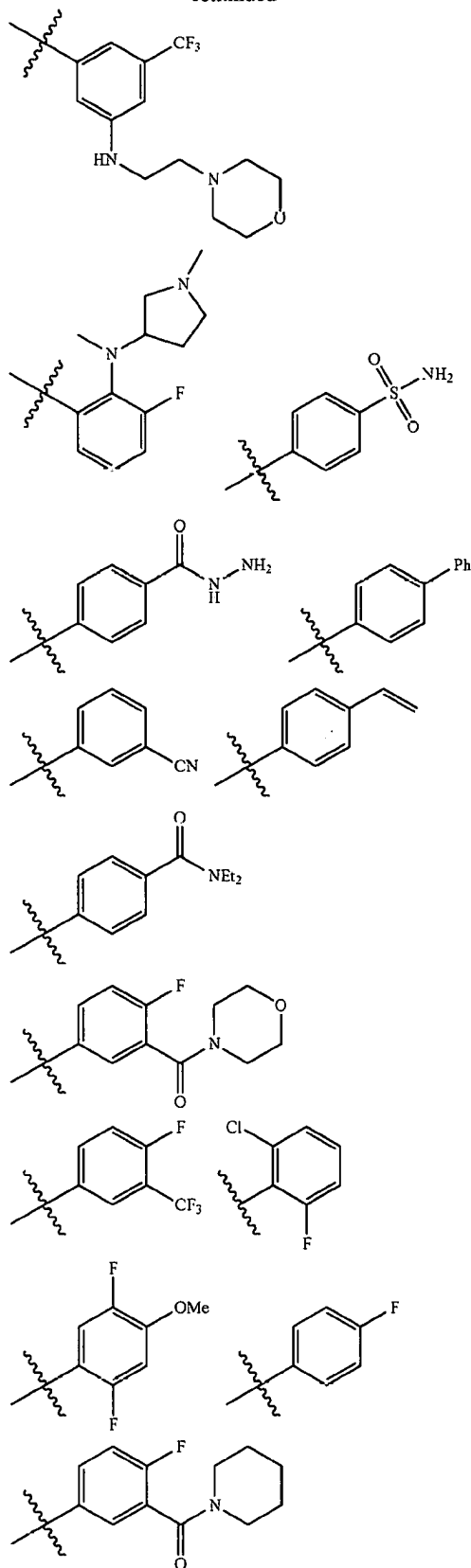
In still another embodiment of any of the above classes and subclasses of compounds, R^a is selected from $-P(=O)(alkyl)_2$, $-(CH_2)_1-2P(=O)(alkyl)_2$, $-O$ -lower alkyl (i.e. OMe and the like), lower alkyl (i.e. methyl, ethyl, cyclopropyl and the like), halo, $-CF_3$, $-OCF_3$, $-CN$, $-NH(alkyl)$, alkenyl, and alkynyl (i.e. acetylene).

Illustrative examples of Phenyl moieties substituted with R^a include, without limitation, the following moieties:



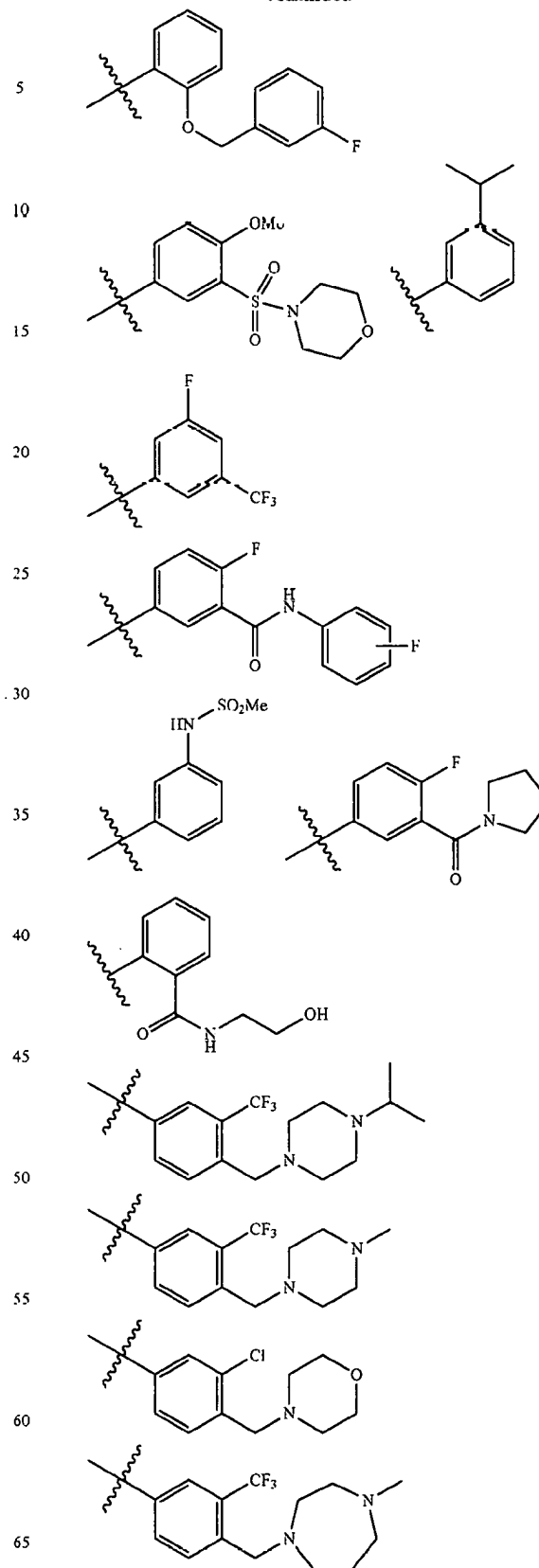
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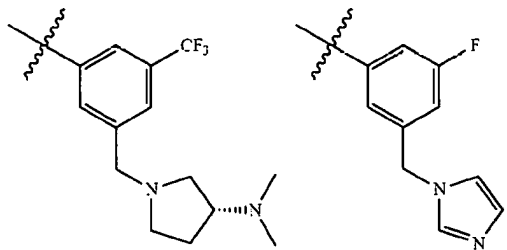
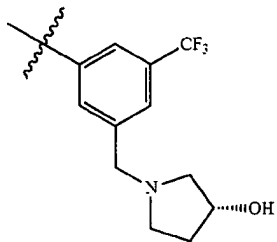
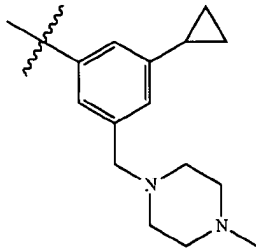
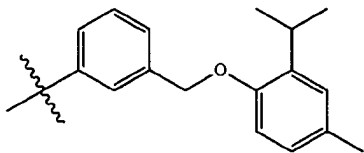
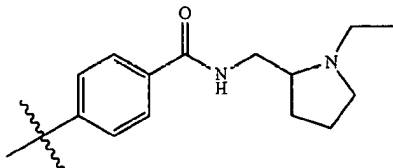
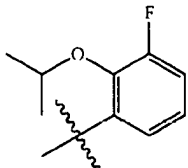
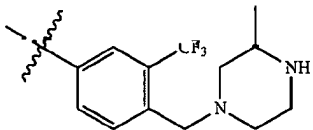
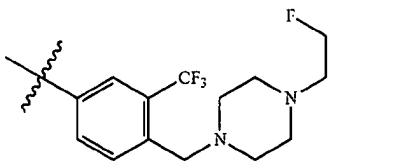
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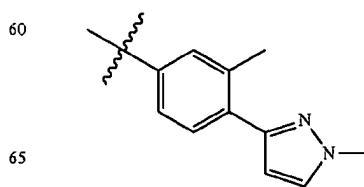
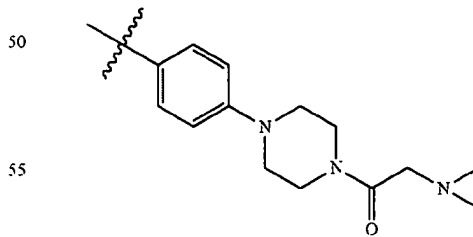
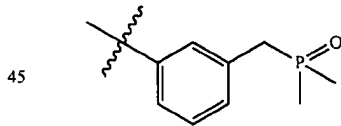
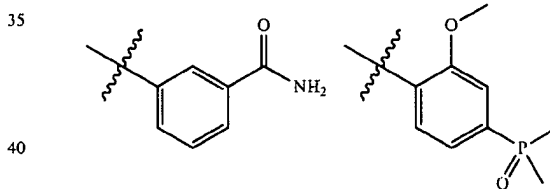
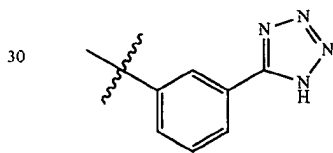
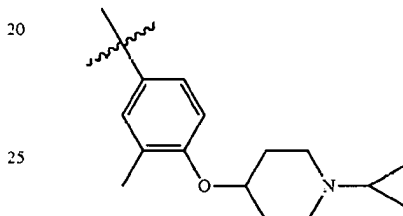
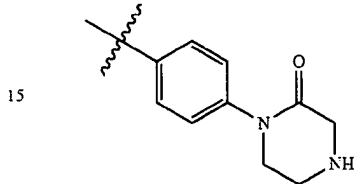
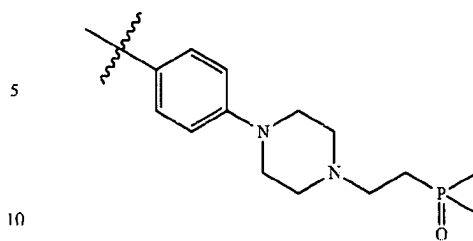
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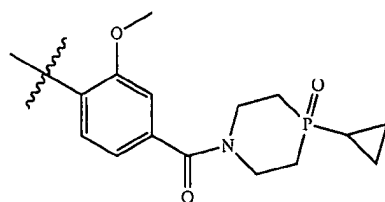
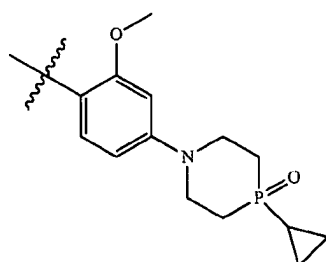
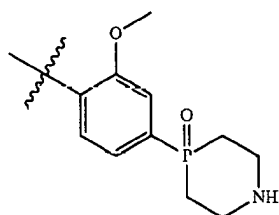
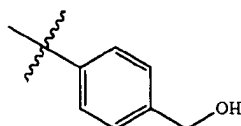
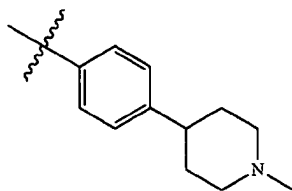
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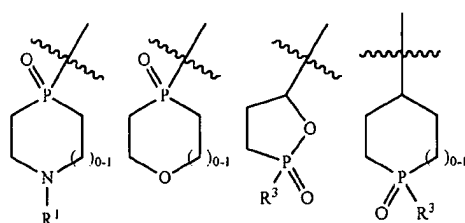


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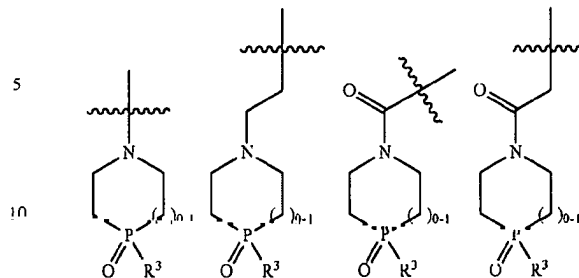


In any of the above classes and subclasses of compounds, R^a is selected from $-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-P(=O)(R^3)_2$, $-(CH_2)_m-O-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-C(=O)-O-P(=O)(R^3)_2$, $-(CH_2)_m-C(=O)-NR^1-P(=O)(R^3)_2$, and $-(CH_2)_m-C(=O)-NR^1-P(=O)(R^3)_2$, in which m is 0, 1, 2, 3 or 4. Alternatively, R^a is a moiety of one of the following formulas:



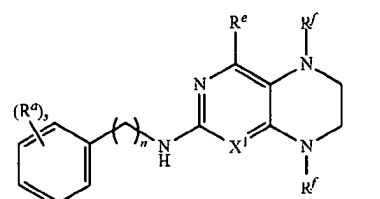
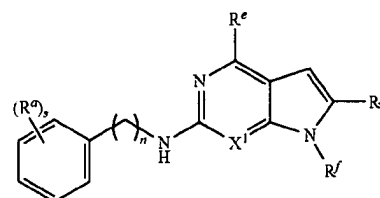
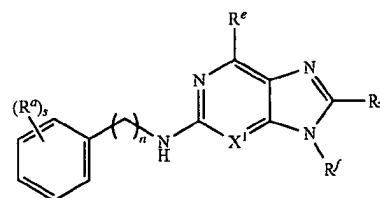
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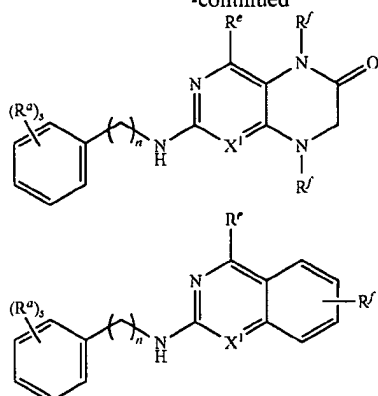
For these classes and other classes and subclasses of the invention, compounds of interest include among others compounds in which one of R^a is or contains $-P(=O)(R^3)_2$. Examples of R^a containing $-P(=O)(R^3)_2$ include, without limitation, $-(CH_2)_m-P(=O)(R^3)_2$, $-(CH_2)_m-O-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-P(=O)(R^3)_2$, $-(CH_2)_m-NR^1-C(=O)-O-P(=O)(R^3)_2$, $-(CH_2)_m-C(=O)-NR^1-P(=O)(R^3)_2$, and $-(CH_2)_m-C(=O)-NR^1-P(=O)(R^3)_2$ in which m is 0, 1, 2, 3 or 4 and cyclic structures containing $-P(=O)$ as depicted above. Of particular current interest are compounds of Formula Ia or VIa in which Ring A is phenyl, X^1 is N, n is 0, s is 2, p is 1, R^e is H and R^d is halo (i.e., F, Cl), lower alkyl (i.e., methyl, ethyl, isopropyl and the like), cyano, nitro, alkoxy (i.e., methoxy and the like) or CF_3 ; one of R^a is or contains $-P(=O)(R^3)_2$ and the other R^a is selected from lower alkyl, halo, cyano and alkoxy (i.e., methoxy); and R^3 is $S(O)_2$ alkyl.

Of other special interest for use in the invention are compounds of formula IIIA in which Ring A is phenyl. Illustrative, non-limiting examples of this subclass are compounds of the formulae:



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Of special interest for use in the invention are compounds of formula IIIA in which one of R^a is or contains —P(=O)(R³)₂ (i.e. CH₂P(=O)Me₂, —P(=O)Me₂, —P(=O)Et₂, —OP(=O)Me₂, —NIIP(=O)Me₂, —NIICH₂P(=O)Et₂ and the like). Of particular current interest are compounds of this subclass in which X¹ is N, n is O, R^a is H and R^f is selected from alkyl, H, aryl, heteroaryl, heterocyclyl, halo (i.e. F, Cl), NHR¹, OR₂, CF₃, SO₂-lower alkyl (i.e. SO₂-iPr and the like), —SO₂-NR¹R² and C(O)NR¹R².

Other compounds of interest include among others, compounds of formula IIIA in which R^f is $-(CH_2)_mP(=O)(alkyl)_2$ (i.e. $-CH_2P(=O)Me_2$, $-P(=O)Me_2$, $-P(=O)Et_2$, etc.). Of particular current interest are compounds of this subclass in which X^1 is N, n is 0, R^g is methoxy, and R^e is H.

Other compounds of interest include among others, compounds of the previous classes and subclasses in which R^d is selected from H, halo (i.e. Chloro, Fluoro, Bromo), $-\text{CF}_3$, optionally substituted lower alkyl group (i.e. Methyl, Ethyl, Isopropyl, Cyclopropyl and the like), $-\text{CN}$, optionally substituted acetylene, $-\text{NO}_2$, $-\text{O-alkyl}$, $-\text{S-alkyl}$, $-\text{C}(=\text{O})\text{alkyl}$, $-\text{NH-alkyl}$ and $-\text{C}(=\text{O})\text{N(alkyl)}_2$. Of further interest are compounds of this class in which R^d is halo or CF_3 .

Other compounds of interest include among others, compounds of the Formula I and IA and of all previous classes and subclasses in which R^e is selected from halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{R}^1$, $-\text{OR}^2$, $-\text{O}-\text{NR}^1\text{R}^2$, $-\text{C}(\text{O})\text{YR}^2$, $-\text{OC}(\text{O})\text{YR}^2$, $-\text{SC}(\text{O})\text{YR}^2$, $-\text{NR}^1\text{C}(=\text{S})\text{YR}^2$, $-\text{OC}(=\text{S})\text{YR}^2$, $-\text{C}(=\text{S})\text{YR}^2$, $-\text{YC}(=\text{NR}^1)\text{YR}^2$, $-\text{YC}(=\text{N}-\text{OR}^1)\text{YR}^2$, $-\text{YC}(=\text{N}-\text{NR}^1\text{R}^2)\text{YR}^2$. Of further interest are compounds of this class in which R^e is H, CN, NO_2 , lower alkyl or halo, wherein R^1 , R^2 , and Y are as defined in Formula I. Of further interest, R^e is selected from I, lower alkyl and halo.

Compounds of the invention of particular interest include those with one or more of the following characteristics:

a molecular weight of less than 1000, preferably less than 750 and more preferably less than 600 mass units (not including the weight of any solvating or co-crystallizing species, of any counter-ion in the case of a salt); or

inhibitory activity against a wild type or mutant (especially a clinically relevant mutant) kinase, especially a kinase such as ALK, Met, Jak2, bRaf, EGFR, Tie-2, FLT3 or another kinase of interest with an IC_{50} value of 1 μ M or less (as determined using any scientifically acceptable kinase inhibition assay), preferably with an IC_{50} of 500 nM or better, and optimally with an IC_{50} value of 250 nM or better; or

inhibitory activity against a given kinase with an IC_{50} value at least 100-fold lower than their IC_{50} values for other kinases of interest; or

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inhibitory activity for ALK, Met, Jak2 or B-Raf with a 1 μ M or better IC_{50} value against each; or

a cytotoxic or growth inhibitory effect on cancer cell lines maintained in vitro, or in animal studies using a scientifically acceptable cancer cell xenograft model, (especially preferred are compounds of the invention which inhibit proliferation of Ba/F3 NMP-ALK, Ba/F3 EML4-ALK, Karpas 299 and/or SU-DIL-1 cells with a potency at least as great as the potency of known ALK inhibitors such as NVP-TAE684 and PF2341066 among others, preferably with a potency at least twice that of known ALK inhibitors, and more preferably with a potency at least 10 times that of known ALK inhibitors as determined by comparative studies.

Also provided is a composition comprising at least one compound of the invention or a salt, hydrate or other solvate thereof, and at least one pharmaceutically acceptable excipient or additive. Such compositions can be administered to a subject in need thereof to inhibit the growth, development and/or metastasis of cancers, including solid tumors (e.g., prostate cancer, colon cancer, pancreatic and ovarian cancers, breast cancer, non small cell lung cancer (NSCLS), neural tumors such as glioblastomas and neuroblastomas; esophageal carcinomas, soft tissue cancers such as rhabdomyosarcomas; among others); various forms of lymphoma such as a non-Hodgkin's lymphoma (NHL) known as anaplastic large-cell lymphoma (ALCL), various forms of leukemia; and including cancers which are resistant to other treatment, including those which are resistant to treatment with another kinase inhibitor, and generally for the treatment and prophylaxis of diseases or undesirable conditions mediated by one or more kinases which are inhibited by a compound of the invention.

The invention features a method for treating cancer. The method includes administering (as a monotherapy or in combination with one or more other anti-cancer agents, one or more agents for ameliorating side effects, radiation, etc) a therapeutically effective amount of a compound of the invention to a human or animal in need of it in order to inhibit, slow or reverse the growth, development or spread of cancer, including solid tumors or other forms of cancer such as leukemias, in the recipient. Such administration constitutes a method for the treatment or prophylaxis of diseases mediated by one or more kinases inhibited by one of the disclosed compounds or a pharmaceutically acceptable derivative thereof. "Administration" of a compound of the invention encompasses the delivery to a recipient of a compound of the sort described herein, or a prodrug or other pharmaceutically acceptable derivative thereof, using any suitable formulation or route of administration, as discussed herein. Typically the compound is administered one or more times per month, often one or more times per week, e.g. daily, every other day, 5 days/week, etc. Oral and intravenous administrations are of particular current interest.

The phrase, "pharmaceutically acceptable derivative", as used herein, denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite (MW>300) thereof which is pharmacologically active as a kinase inhibitor. Pharmaceutically acceptable derivatives thus include among others pro-drugs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety which is susceptible to removal in vivo yielding the parent molecule as the pharmacologically active species. An example of a pro-drug

is an ester which is cleaved *in vivo* to yield a compound of interest. Pro-drugs of a variety of compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the invention.

Particularly favored derivatives and prodrugs of a parent compound are those derivatives and prodrugs that increase the bioavailability of the compound when administered to a mammal (e.g., by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a biological compartment of interest (e.g., the brain or lymphatic system) relative to the parent compound. Preferred prodrugs include derivatives of a compound of the invention with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

One important aspect of the invention is a method for treating cancer in a subject in need thereof, which comprises administering to the subject a treatment effective amount of a composition containing a compound of the invention. Treatment may be provided in combination with one or more other cancer therapies, include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, etc.), endocrine therapy, biologic response modifiers (e.g., interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia, cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other cancer chemotherapeutic drugs. The other agent(s) may be administered using a formulation, route of administration and dosing schedule the same or different from that used with the compound of the invention.

Such other drugs include but not limited to one or more of the following: an anti-cancer alkylating or intercalating agent (e.g., mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, and Ifosfamide); antimetabolite (e.g., Methotrexate); purine antagonist or pyrimidine antagonist (e.g., 6-Mercaptopurine, 5-Fluorouracil, Cytarabine, and Gemcitabine); spindle poison (e.g., Vinblastine, Vincristine, Vinorelbine and Paclitaxel); podophyllotoxin (e.g., Etoposide, Irinotecan, Topotecan); antibiotic (e.g., Doxorubicin, Bleomycin and Mitomycin); nitrosourea (e.g., Carmustine, Lomustine); inorganic ion (e.g., Cisplatin, Carboplatin, Oxaliplatin or oxiplatin); enzyme (e.g., Asparaginase); hormone (e.g., Tamoxifen, Leuprolide, Flutamide and Megestrol); mTOR inhibitor (e.g., Sirolimus (rapamycin), Temsirolimus (CCI779), Everolimus (RAD001), AP23573 or other compounds disclosed in U.S. Pat. No. 7,091,213); proteasome inhibitor (such as Velcade, another proteasome inhibitor (see e.g., WO 02/096933) or another NF- κ B inhibitor, including, e.g., an I κ K inhibitor); other kinase inhibitors (e.g., an inhibitor of Src, BCR/Abi, kdr, flt3, aurora-2, glycogen synthase kinase 3 ("GSK-3"), EGF-R kinase (e.g., Iressa, Tarceva, etc.), VEGF-R kinase, PDGF-R kinase, etc.); an antibody, soluble receptor or other receptor antagonist against a receptor or hormone implicated in a cancer (including receptors such as EGFR, ErbB2, VEGFR, PDGFR, and IGF-R; and agents such as Herceptin, Avastin, Erbitux, etc.); etc. For a more comprehensive discussion of updated cancer therapies see, <http://www.nci.nih.gov/>, a list of the FDA approved oncology drugs at <http://www.fda.gov/cder/cancer/druglistframe.htm>, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference. Examples of other therapeutic agents are noted elsewhere herein and include among others, Zylloprim, alemtuzumab, altretamine, amifostine, nastrozole, antibodies against prostate-specific membrane antigen (such as MLN-591, MLN591RL and MLN2704), arsenic trioxide, bexarotene, bleomycin, busulfan, capecitabine, Gliadel Wafer, celecoxib, chlorambucil,

cisplatin-epinephrine gel, cladribine, cytarabine liposomal, daunorubicin liposomal, daunorubicin, daunomycin, dexrazoxane, docetaxel, doxorubicin, Elliott's B Solution, epirubicin, estramustine, etoposide phosphate, etoposide, exemestane, fludarabine, 5-FU, fulvestrant, gemcitabine, gemtuzumab-ozogamicin, goserelin acetate, hydroxyurea, idarubicin, idarubicin, Idamycin, ifosfamide, imatinib mesylate, irinotecan (or other topoisomerase inhibitor, including antibodies such as MLN576 (XR11576)), letrozole, leucovorin, leucovorin levamisole, liposomal daunorubicin, melphalan, L-PAM, mesna, methotrexate, methoxsalen, mitomycin C, mitoxantrone, MLN518 or MLN608 (or other inhibitors of the flt-3 receptor tyrosine kinase, PDGF-R or c-kit), itoxantrone, paclitaxel, Pegademase, pentostatin, porfimer sodium, Rituximab (RITUXAN®), talc, tamoxifen, temozolamide, teniposide, VM-26, topotecan, toremifene, 2C4 (or other antibody which interferes with HER2-mediated signaling), tretinoin, ATRA, valrubicin, vinorelbine, or pamidronate, zoledronate or another bisphosphonate.

The invention further comprises the preparation of a compound of any of Formulae I, Ia, II, IIa, III, IIIc, IV, IVa, V, Va, VI, VIa VII, VIIa and VIIb or of any other of compounds of the invention using a method described herein.

The invention also comprises the use of a compound of the invention, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment either acutely or chronically of cancer (including lymphoma and solid tumors, primary or metastatic, including cancers such as noted elsewhere herein and including cancers which are resistant or refractory to one or more other therapies). Compounds of the invention can be useful in the manufacture of an anti-cancer medicaments. Compounds of the invention can also be useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of one or more kinases such as ALK, jak2, b-raf, met, Tie-2, EGFR, FLT3, FAK, Pim-1, PI3k, etc.

The invention further encompasses a composition comprising a compound of the invention, including a compound of any of the described classes or subclasses, including those of any of the formulas noted above, among others, preferably in a therapeutically-effective amount, in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

Compounds of the invention can also be useful as standards and reagents for characterizing various kinases, especially but not limited to ALK, Met, Jak2, b-Raf, Tie-2, EGFR, FLT3 among others as well as for studying the role of such kinases in biological and pathological phenomena; for studying intracellular signal transduction pathways mediated by such kinases, for the comparative evaluation of new kinase inhibitors; and for studying various cancers in cell lines and animal models.

3. Definitions

In reading this document, the following information and definitions apply unless otherwise indicated.

The term "alkyl" is intended to include linear (i.e., unbranched or acyclic), branched, cyclic, or polycyclic non aromatic hydrocarbon groups, which are optionally substituted with one or more functional groups. Unless otherwise specified, "alkyl" groups contain one to eight, and preferably one to six carbon atoms. C₁₋₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ alkyl groups. Lower alkyl refers to alkyl groups containing 1 to 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl,

cyclobutyl, pentyl, isopentyl tert-pentyl, cyclopentyl, hexyl, isohexyl, cyclohexyl, etc. Alkyl may be substituted or unsubstituted. Illustrative substituted alkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl, substituted benzyl, phenethyl, substituted phenethyl, etc.

The term "alkoxy" represents a subset of alkyl in which an alkyl group as defined above with the indicated number of carbons attached through an oxygen bridge. For example, "alkoxy" refers to groups —O-alkyl, wherein the alkyl group contains 1 to 8 carbon atoms of a linear, branched, cyclic configuration. Examples of "alkoxy" include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, t-butoxy, n-butoxy, s-pentoxyl and the like.

"Haloalkyl" is intended to include both branched and linear chain saturated hydrocarbon having one or more carbon substituted with a Halogen. Examples of haloalkyl, include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl and the like.

The term "alkenyl" is intended to include hydrocarbon chains of linear, branched, or cyclic configuration having one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain or cycle. Unless otherwise specified, "alkenyl" refers to groups usually having two to eight, often two to six carbon atoms. For example, "alkenyl" may refer to prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, hex-5-enyl, 2,3-dimethylbut-2-enyl, and the like. Furthermore, alkenyl groups may be substituted or unsubstituted.

The term "alkynyl" is intended to include hydrocarbon chains of either linear or branched configuration, having one or more carbon-carbon triple bond that may occur in any stable point along the chain. Unless otherwise specified, "alkynyl" groups refer refers to groups having two to eight, preferably two to six carbons. Examples of "alkynyl" include, but are not limited to prop-2-ynyl, but-2-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl, hex-5-ynyl, etc. Furthermore, alkynyl groups may be substituted or unsubstituted.

Cycloalkyl is a subset of alkyl and includes any stable cyclic or polycyclic hydrocarbon groups of from 3 to 13 carbon atoms, any of which is saturated. Examples of such cycloalkyl include, but are not limited to cyclopropyl, norbornyl, [2.2.2]bicyclooctane, [4.4.0]bicyclodecane, and the like, which, as in the case of other alkyl moieties, may optionally be substituted. The term "cycloalkyl" may be used interchangeably with the term "carbocycle".

Cycloalkenyl is a subset of alkenyl and includes any stable cyclic or polycyclic hydrocarbon groups of from 3 to 13 carbon atoms, preferably from 5 to 8 carbon atoms, which contains one or more unsaturated carbon-carbon double bonds that may occur in any point along the cycle. Examples of such cycloalkenyl include, but are not limited to cyclopentenyl, cyclohexenyl and the like.

Cycloalkynyl is a subset of alkynyl and includes any stable cyclic or polycyclic hydrocarbon groups of from 5 to 13 carbon atoms, which contains one or more unsaturated carbon-carbon triple bonds that may occur in any point along the cycle. As in the case of other alkenyl and alkynyl moieties, cycloalkenyl and cycloalkynyl may optionally be substituted.

The term "heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 7 carbon atoms in addition to 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O, S, and P. Heteroalkyls include, without limitation, tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, car-

bamates, thiocarbamates, hydrazones, imines, phosphodiesteres, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. The heteroalkyl group may be substituted or unsubstituted. Examples of heteroalkyls include, without limitation, polyethers, such as methoxymethyl and ethoxyethyl.

"Heterocycle", "heterocyclyl", or "heterocyclic" as used herein refers to non-aromatic ring systems having five to fourteen ring atoms in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Heterocyclic groups may be substituted or unsubstituted and may include one, two, or three fused or unfused ring systems. Non-limiting examples of heterocyclic rings include 3-1H-benzimidazol-2-one, (1-substituted)-2-oxobenzimidazol-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl. A heterocyclic group can include two or more of the ring systems listed above. Also included within the scope of the term "heterocyclyl" or "heterocyclic", as it is used herein, is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The term "heterocycle", "heterocyclyl", or "heterocyclic" whether saturated or partially unsaturated, also refers to rings that are optionally substituted.

The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to aromatic ring groups having six to fourteen ring atoms, such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. An "aryl" ring may contain one or more substituents. The term "aryl" may be used interchangeably with the term "aryl ring". "Aryl" also includes fused polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Non-limiting examples of useful aryl ring groups include phenyl, hydroxyphenyl, halophenyl, alkoxyphenyl, dialkoxyphenyl, trialkoxyphenyl, alkylenedioxyphenyl, naphthyl, phenanthryl, anthryl, phenanthro and the like, as well as 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in an indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

The term "heteroaryl" as used herein refers to stable heterocyclic, and polyheterocyclic aromatic moieties having 5-14 ring atoms. Heteroaryl groups may be substituted or unsubstituted and may comprise one or more rings. Examples of typical heteroaryl rings include 5-membered monocyclic ring groups such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl and the like; 6-membered monocyclic groups such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like; and polycyclic heterocyclic ring groups such as benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathieryl, indoliziny, isindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl,

phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, benzothiazole, benzimidazole, tetrahydroquinoline cinnolinyl, pteridinyl, carbazoyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthroline, phenazinyl, isothiazolyl, phenothiazinyl, phloxazinyl, and the like (see e.g. Katritzky, Handbook of Heterocyclic Chemistry). Further specific examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-triazolyl, 5-triazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzoisoxazolyl. Heteroaryl groups further include a group in which a heteroaromatic ring is fused to one or more aromatic or nonaromatic rings where the radical or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinolino, tetrahydroisoquinolino, and pyrido[3,4-d]pyrimidinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-c]pyrimidinyl, pyrazolo[1,5-a][1,3,5]triazinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,5-a]pyrimidinyl, pyrazolo[1,5-b][1,2,4]triazine, quinolyl, isoquinolyl, quinoxalyl, imidazotriazinyl, pyrrolo[2,3-d]pyrimidinyl, triazolopyrimidinyl, pyridopyrazinyl. The term "heteroaryl" also refers to rings that are optionally substituted. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

An aryl group (including the aryl portion of an aralkyl, aralkoxy, or aryloxyalkyl moiety and the like) or heteroaryl group (including the heteroaryl portion of a heteroaralkyl or heteroarylalkoxy moiety and the like) may contain one or more substituents. Examples of suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group include halogen (F, Cl, Br or I), alkyl, alkenyl, alkynyl, heteroalkyl, CN, OR², S(O)_rR², (wherein r is an integer of 0, 1 or 2), —SO₂NR¹R², —NR¹R², —O—NR¹R², —NR¹R², —(CO)YR², —O(CO)YR², —NR¹(CO)YR², —S(CO)YR², —YR¹C(=S)YR², —OC(=S)YR², —C(=S)YR², wherein each occurrence of Y is independently —O—, —S—, —NR¹—, or a chemical bond; —(CO)YR² thus encompasses —C(=O)R², —C(=O)OR², and

C(=O)NR¹R². Additional substituents include YC(=NR¹)YR², —YC(=N—OR¹)YR², —YC(=N—NR¹R²)YR², —COCOR², —COMCOR² (where M is a 1-6 carbon alkyl group), —YP(=O)(YR³)(YR³) (including among others —P(=O)(R³)₂), —Si(R³)₃, —NO₂, —NR¹SO₂R² and —NR¹SO₂NR¹R². To illustrate further, substituents in which Y is —NR¹ thus include among others, —NR¹C(=O)R²,

NR¹C(=O)NR¹R², NR¹C(=O)OR², and NR¹C(=NH)NR¹R². R³ substituent is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl; R¹ and R² substituents at each occurrence are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, and R¹, R² and R³ substituents may themselves be substituted or unsubstituted. Examples of substituents allowed on R¹, R² and R³ include, among others amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, aryl, heteroalkyl, heteroaryl, carbocycle, heterocycle, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, alkoxy, haloalkoxy

groups. Additional illustrative examples include protected OH (such as acyloxy), phenyl, substituted phenyl, —O-phenyl, —O— (substituted) phenyl, —benzyl, substituted benzyl, —O-phenethyl (i.e., —OCH₂CH₂C₆H₅), —O— (substituted) phenethyl. Non-limiting illustrations of a substituted R¹, R² or R³ moiety include haloalkyl and trihaloalkyl, alkoxyalkyl, haloalkenyl, —M-heteroaryl, —M-heterocycle, —M-aryl, —M-OR², —M-SR², —M-NR¹R², —M-OC(O)NR¹R², —M-C(=NR¹)NR¹R², —M-C(=NR¹)OR², —M-P(=O)(R³)₂, Si(R³)₃, —M-NR¹C(O)R², —M-NR¹C(O)OR², —M-C(O)R², —M-C(=S)R², —M-C(=S)NR¹R², —M-C(O)NR¹R², —M-C(O)NR¹R², —M-NR¹R², —M-NR¹C(NR¹)NR¹R², —M-NR¹C(S)NR¹R², —M-S(O)₂R¹, —M-C(O)R¹, —M-OC(O)R¹, —MC(O)SR², —M-S(O)₂NR¹R², —C(O)—M-C(O)R², —MCO₂R², —MC(=O)NR¹R², —M-C(=N)NR¹R², and —M-OC(=N)NR¹R² (wherein M is a 1-6 carbon alkyl group).

Some more specific examples include but are not limited to chloromethyl, trichloromethyl, trifluoromethyl, methoxyethyl, alkoxyphenyl, haloalkenyl, —CH₂-aryl, —CH₂-heterocycle, —CH₂C(O)NH₂, —C(O)CH₂N(CH₃)₂, —CH₂CH₂OH, —CH₂OC(O)NH₂, —CH₂CH₂NH₂, —CH₂CH₂CH₂NEt₂, —CH₂OCH₃, —C(O)NH₂, —CH₂CH₂-heterocycle, —C(=S)CH₃, —C(=S)NH₂, —C(=NH)NH₂, —C(=NH)OEt, —C(O)NH-cyclopropyl, —C(O)NHCH₂CH₂-heterocycle, —C(O)NHCH₂CH₂OCH₃, —C(O)CH₂CH₂NHCH₃, —CH₂CH₂F, —C(O)CH₂-heterocycle, —CH₂C(O)NHCH₃, —CH₂CH₂P(=O)(CH₃)₂, Si(CH₃)₃ and the like.

When a ring system (e.g., cycloalkyl, heterocyclyl, aryl, or heteroaryl) is substituted with a number of substituents varying within an expressly defined range, it is understood that the total number of substituents does not exceed the normal available valencies under the existing conditions. Thus, for example, a phenyl ring substituted with "n" substituents (where "n" ranges from 1 to 5) can have 1 to 5 substituents, whereas it is understood that a pyridinyl ring substituted with "n" substituents has a number of substituents ranging from 1 to 4. The maximum number of substituents that a group in the compounds of the invention may have can be easily determined.

An alkyl, alkenyl, alkynyl, alkoxy, haloalkyl, heteroalkyl, cycloalkyl, cycloalkenyl, cycloalkynyl or non-aromatic heterocyclic group may thus also contain one or more substituents. Examples of suitable substituents on such groups include, but are not limited to those listed above for the carbon atoms of an aryl or heteroaryl group and in addition include the following substituents for a saturated carbon atom: =O, =S, =NH, =NNR²R³, =NNHC(O)R², =NNHCO₂R², or =NNHSO₂R², wherein R² and R³ at each occurrence are independently hydrogen, alkyl, alkenyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, aryl, heteroaryl, heterocyclyl.

Illustrative examples of substituents on an aliphatic, heteroaliphatic or heterocyclic group include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, —CN, carboxy, alkoxycarbonyl, alkylcarbonyl, —OH, haloalkoxy, or haloalkyl groups.

Illustrative substituents on a nitrogen, e.g., in an heteroaryl or non-aromatic heterocyclic ring include R¹, —NR¹R², —C(=O)R², —C(=O)OR², —C(=O)SR², —C(=O)NR¹R², —C(=NR¹)NR¹R², —C(=NR¹)OR², —C(=NR¹)R³, —COCOR², —COMCOR², —CN, —SO₂R², S(O)R², —P(=O)(YR³)(YR³), —NR¹SO₂R² and —NR¹SO₂NR¹R², wherein each occurrence of R³ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and

heterocyclyl; each occurrence of R¹ and R² is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocyclyl.

When a ring system (e.g., cycloalkyl, heterocyclyl, aryl, or heteroaryl) is substituted with a number of substituents varying within an expressly defined range, it is understood that the total number of substituents does not exceed the normal available valencies under the existing conditions. Thus, for example, a phenyl ring substituted with "m" substituents (where "m" ranges from 0 to 5) can have 0 to 5 substituents, whereas it is understood that a pyridinyl ring substituted with "m" substituents has a number of substituents ranging from 0 to 4. The maximum number of substituents that a group in the compounds of the invention may have can be easily determined.

Certain compounds of the invention may exist in tautomeric forms, and the invention includes all such tautomeric forms of those compounds unless otherwise specified.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Thus, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Thus, the invention encompasses each diastereomer or enantiomer substantially free of other isomers (>90%, and preferably >95%, free from other stereoisomers on a molar basis) as well as a mixture of such isomers.

Particular optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound.

Optically active compounds of the invention can be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Compounds of the invention can exist in radiolabelled form, i.e., said compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number ordinarily found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine and chlorine include ³H, ¹⁴C, ³²P, ³⁵S, ¹⁸F and ³⁶Cl, respectively. Compounds of the invention which contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of the invention. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, radioisotopes are particularly preferred for their ease of preparation and detectability.

Radiolabelled compounds of the invention can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabelled compounds can be prepared by carrying out the procedures disclosed herein except substituting a readily available radiolabelled reagent for a non-radiolabelled reagent.

4. Synthetic Overview

The practitioner has a well-established literature of heterocyclic and other relevant chemical transformations, recovery and purification technologies to draw upon, in combination with the information contained in the examples which follow, for guidance on synthetic strategies, protecting groups, and other materials and methods useful for the synthesis, recovery and characterization of compounds of the invention, including compounds containing the various choices for the R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, R^l, R^m, Rⁿ, R^o, R^p, R^q, R^r, R^s, R^t, R^u, R^v, R^w, R^x, R^y, R^z, and Rings A, B, C, D, E and F.

Various synthetic approaches may be used to produce the compounds described herein, including those approaches depicted schematically below. The practitioner will appreciate that protecting groups may be used in these approaches. "Protecting groups", are moieties that are used to temporarily block chemical reaction at a potentially reactive site (e.g., an amine, hydroxy, thiol, aldehyde, etc.) so that a reaction can be carried out selectively at another site in a multifunctional compound. In preferred embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is suitable for the planned reactions; the protecting group should be selectively removable in good yield by readily available, preferably nontoxic reagents that do not unduly attack the other functional groups present; the protecting group preferably forms an readily separable derivative (more preferably without the generation of new stereogenic centers); and the protecting group preferably has a minimum of additional functionality to avoid the complication of further sites of reaction. A wide variety of protecting groups and strategies, reagents and conditions for deploying and removing them are known in the art. See, e.g., "Protective Groups in Organic Synthesis" Third Ed. Greene, T. W. and Wuts, P. G., Eds., John Wiley & Sons, New York: 1999. For additional background information on protecting group methodologies (materials, methods and strategies for protection and deprotection) and other synthetic chemistry transformations useful in producing the compounds described herein, see in R. Larock, Comprehensive organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995). The entire contents of these references are hereby incorporated by reference.

Also, one may chose reagents enriched for a desired isotope, e.g. deuterium in place of hydrogen, to create compounds of the invention containing such isotope(s). Compounds containing deuterium in place of hydrogen in one or more locations, or containing various isotopes of C, N, P and O, are encompassed by the invention and may be used, for instance, for studying metabolism and/or tissue distribution of the compounds or to alter the rate or path of metabolism or other aspects of biological functioning.

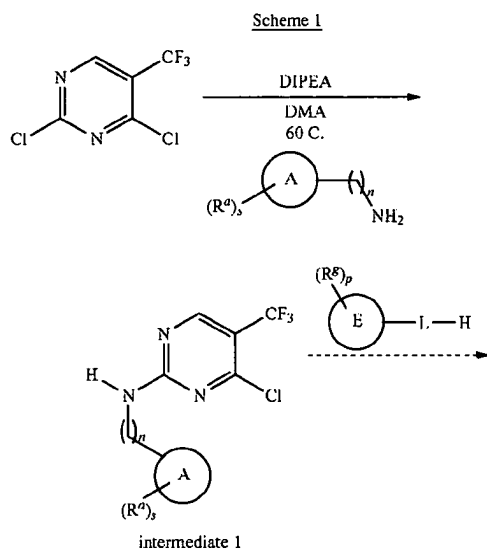
Compounds of the invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by a variation thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to those described below. The reactions are preformed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent the transformations proposed. This will sometimes required

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some judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

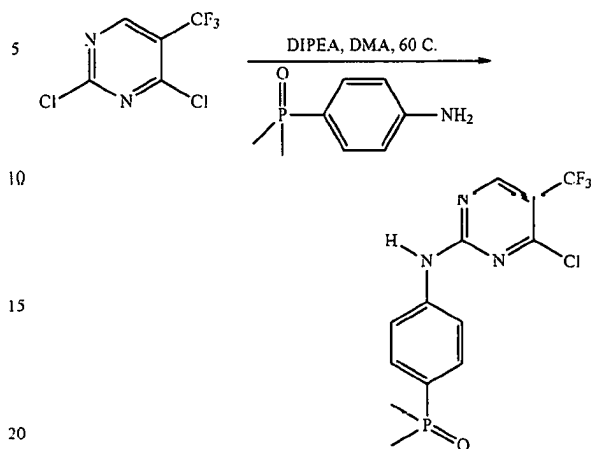
A compound of the invention could be prepared as outlined from Scheme 1 to Scheme 57a and via standard methods known to those skilled in the art. For certain compounds of the invention, microwave-assisted synthesis may be carried out using conventional procedures and the conditions noted in the examples which follow. Reactions may be carried out using commercially available microwave reactors such as the Biotage Initiator 2.0™ (Biotage AB, Kungsgatan 76, SE-753 18 Uppsala, Sweden or 1725 Discovery Drive Charlottesville, Va. 22911) or the CEM Discover™ System (CEM Corporation, Matthews, N.C.) which were used in the examples below.

A compound of Formula Ia or VIA in which n is 0 and X is N can be prepared in a 2 steps synthesis as shown in Scheme 1. A [Ring A] moiety can first be incorporated to the central pyrimidine moiety by reacting [Ring A]-NH₂ with 2,4-dichloro-5-(trifluoromethyl)pyrimidine in the presence of a base such as di-isopropylethyl amine at high temperature generating intermediate 1. The [Ring E]-L moiety can then be incorporated onto intermediate 1 using various conditions depending on the nature of the L linker. The variables in the intermediate [Ring E]-[L]- and [Ring A] are as defined previously, Rings A and E being substituted with permitted R^a and R^g groups respectively.

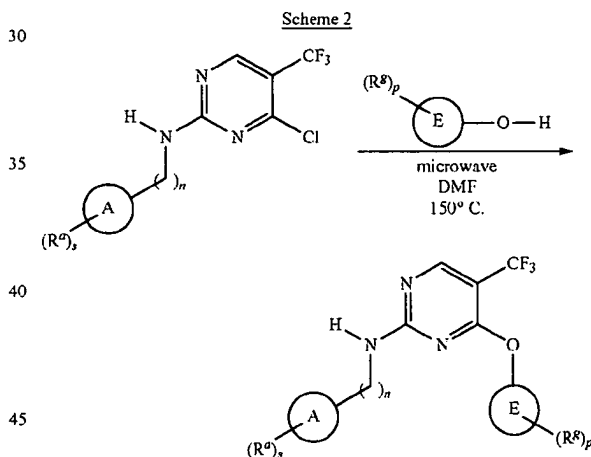


An approach to the preparation of an intermediate 1 is illustrated below in Scheme 1A in which Ring A is a phenyl:

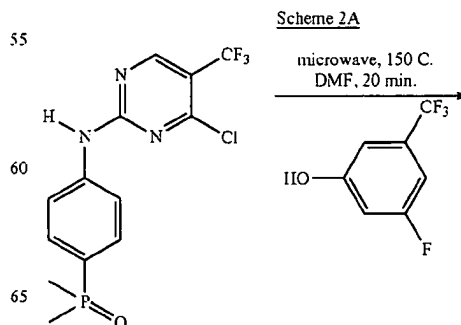
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Scheme 1A

A compound of Formula VIA in which L is O can be prepared using microwave chemistry, by reacting an intermediate 1 with [Ring E]-OH in a solvent such as dimethylformamide and high temperatures as shown in Scheme 2.

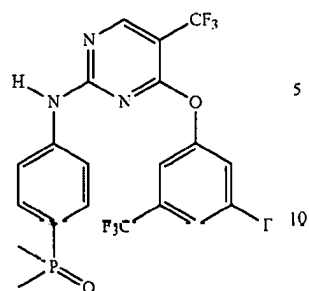


An approach to the preparation of a compound of Formula VIA in which L is O, is illustrated below in Scheme 2A in which Ring A and Ring E are phenyls:



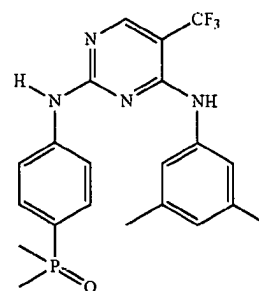
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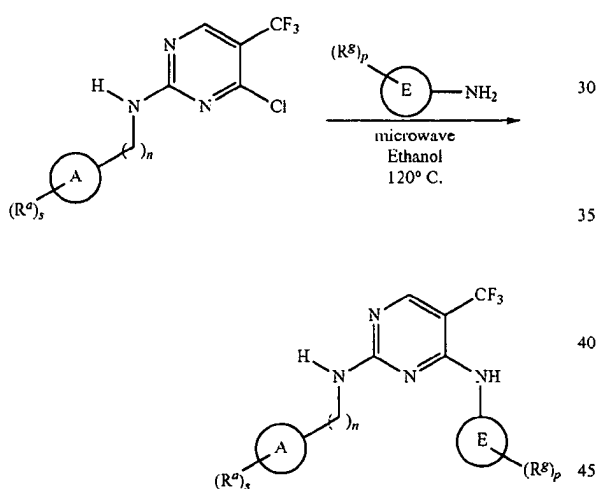
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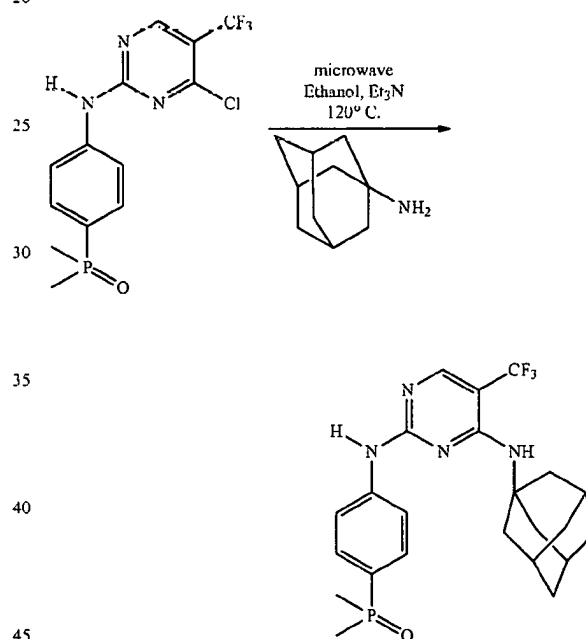


A compound of Formula VIA in which L is NH can be prepared using microwave chemistry, by reaction an intermediate 1 with [Ring E]-NH₂, in a polar solvent such as Ethanol, and using high temperatures, as shown in Scheme 3. A base (i.e. di-isopropylethyl amine, triethylamine or the like) or an acid may be added to facilitate the displacement reaction.

Scheme 3

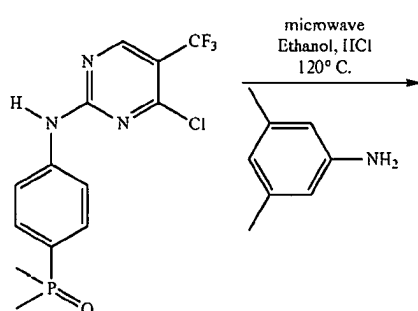


Scheme 3B



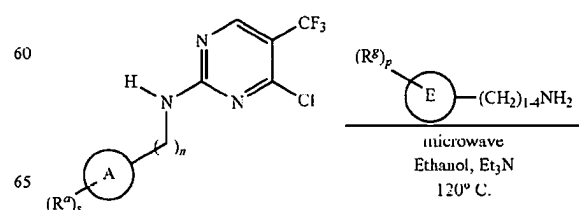
An approach to the preparation of a few compounds of Formula VIA in which L is NH, is illustrated below in Scheme 3A and 3B in which E is a phenyl or adamantanamine:

Scheme 3A



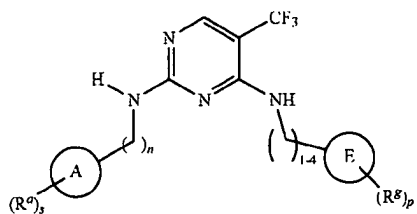
A compound of Formula VIA in which L is NH(CH₂)₁₋₄ can be prepared using microwave chemistry, by reaction an intermediate 1 with [Ring E]-(CH₂)₁₋₄NH₂, in the presence of a base such as triethylamine, in a polar solvent such as Ethanol, and using high temperatures, as shown in Scheme 4:

Scheme 4



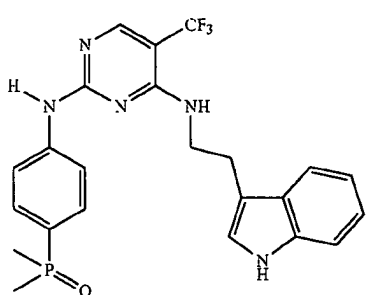
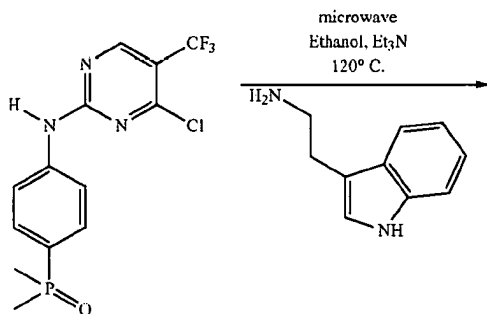
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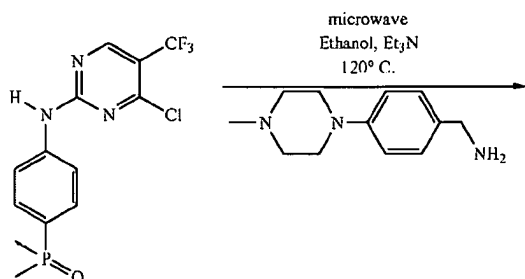


An approach to the preparation of a few compounds of Formula VIA in which L is $\text{NH}(\text{CH}_2)_{1-4}$, is illustrated below in Schemes 4A and 4B. Scheme 4A illustrates the synthesis of a compound of Formula VIA in which E is a phenyl and L is NHCH_2 and Scheme 4B illustrates the synthesis of a compound of Formula VIA in which E is 3-1H-indole and L is $\text{NH}(\text{CH}_2)_2$:

Scheme 4A



Scheme 4B



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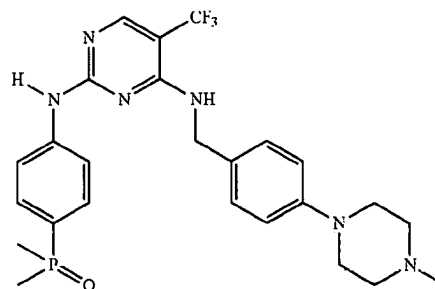
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A compound of Formula VIA in which L is $\text{SH}(\text{CH}_2)_y$ can be prepared using microwave chemistry, by reaction an intermediate 1 with $[\text{Ring E}]-(\text{CH}_2)_y\text{SH}$, in the presence of a base such as Cesium carbonate, and in a solvent such as dimethylformamide at high temperatures, as shown in Scheme 5. The variable y is defined above.

Scheme 5

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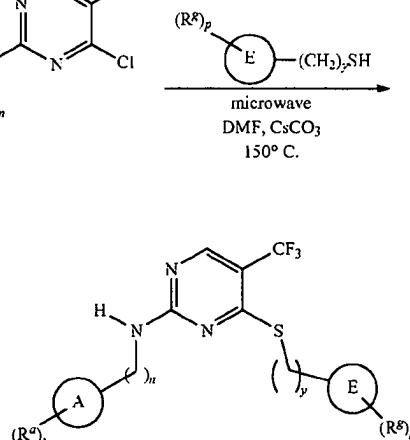
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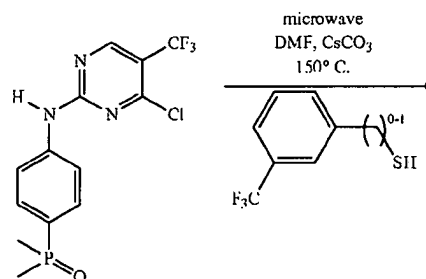
An approach to the preparation of a compound of Formula VIA in which L is $\text{S}(\text{CH}_2)_y$, is illustrated below in Scheme 5A:

Scheme 5A

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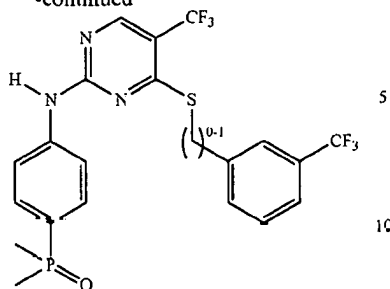
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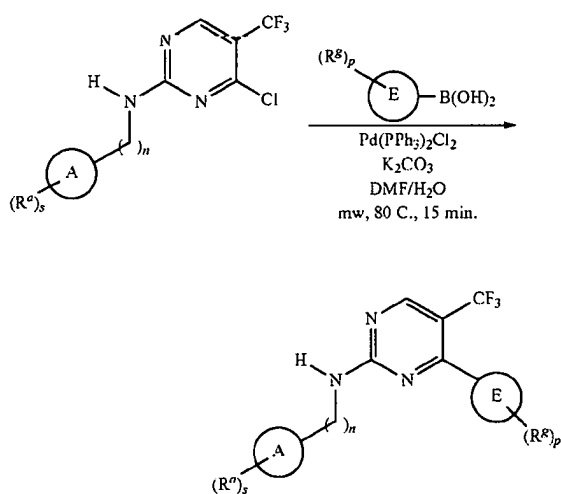
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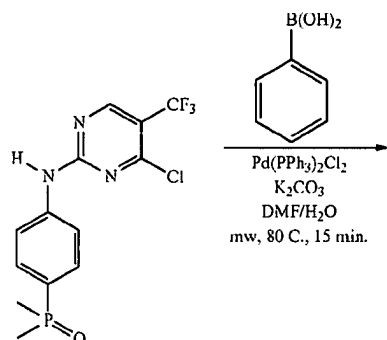
A compound of Formula VIA in which L is bond and [Ring E] is an aryl or heteroaryl, can be prepared using Suzuki coupling conditions. Scheme 6 illustrates the Suzuki coupling reaction.

Scheme 6



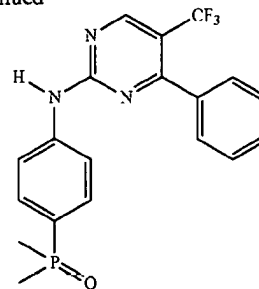
In a non limiting example, Scheme 6A illustrates the preparation of a compound of Formula VIA in which L is a bond and [Ring E] is a phenyl.

Scheme 6A



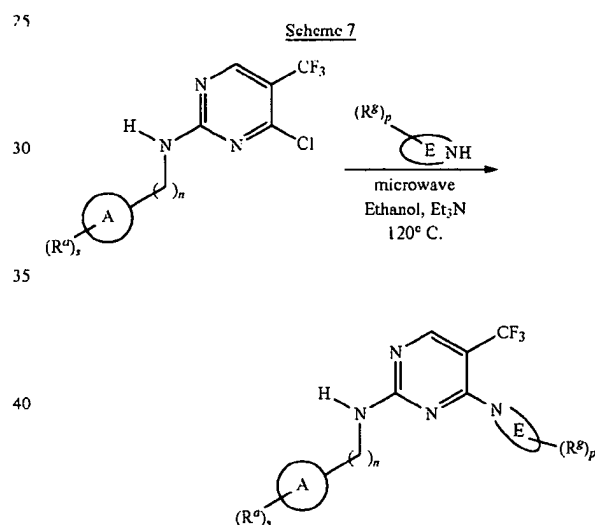
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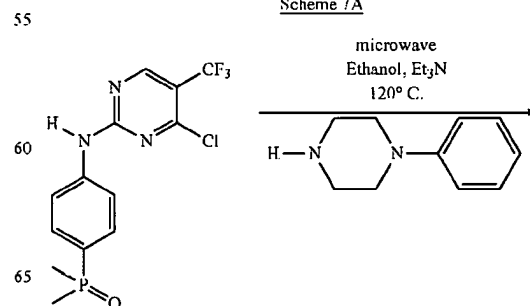
A compound of Formula VIA in which L is bond and [Ring E] is a N-linked heterocyclyl, can be prepared using microwave chemistry, by reaction an intermediate 1 with the heterocyclyl, in the presence of a base such as triethylamine, in a polar solvent such as Ethanol, and using high temperatures, as shown in Scheme 7:

Scheme 7



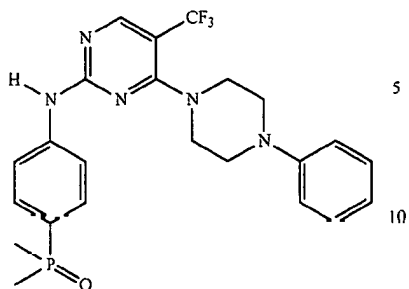
In a non limiting example, Scheme 7A illustrates the preparation of a compound of Formula VIA in which L is a bond and [Ring E] is N-phenyl-piperazine.

Scheme 7A



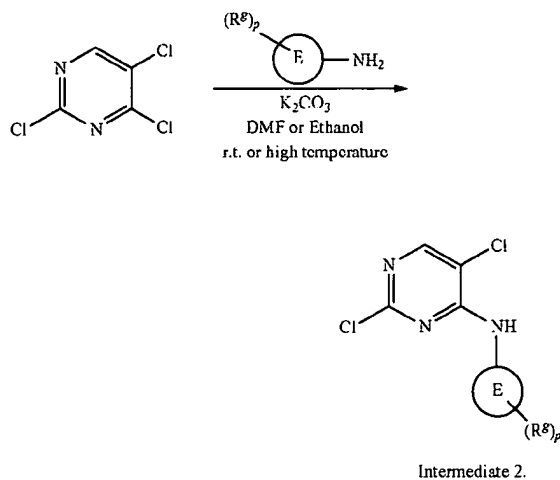
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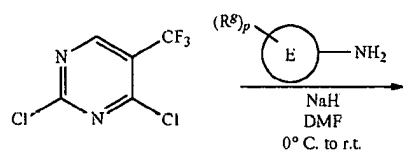
An alternative reaction sequence can be used for the preparation of compounds of Formula VIa in which L is NH. [Ring E]-NH moiety can be first incorporated to the central pyrimidine moiety prior to the incorporation of [Ring A]-NH moiety. Scheme 8 illustrates the reaction of 2,4,5-trichloropyrimidino with a [Ring-E]-NH₂ moiety in the presence of a base (i.e. potassium carbonate or sodium hydride or the like) in a solvent such as dimethylformamide or Ethanol in order to generate intermediate 2. The reaction can be performed at room temperature or may require higher temperature.

Scheme 8



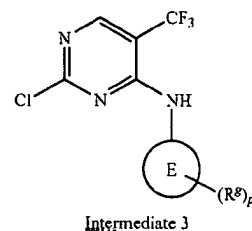
Another example of this reaction is shown below in Scheme 9 in which intermediate 3 is prepared by reacting 2,4-dichloro-5-(trifluoromethyl)pyrimidine with a [Ring E]-NH₂ moiety in the presence of sodium hydride in dimethylformamide at lower temperatures.

Scheme 9



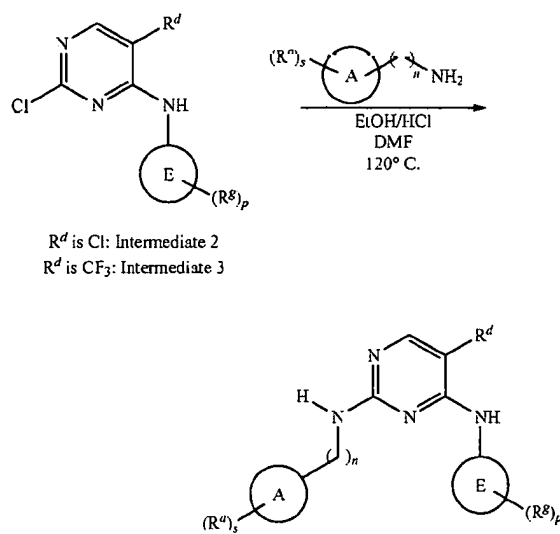
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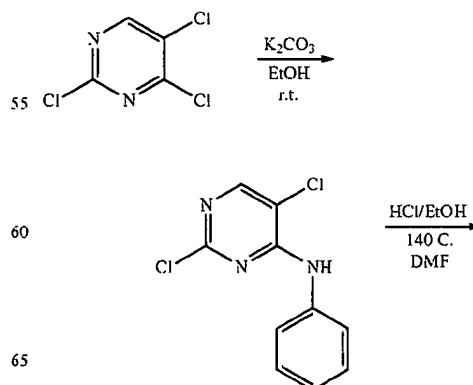
Intermediate 2 or 3 can then be reacted with a [Ring-A]-(CH₂)_nNH₂ moiety using regular displacement conditions as shown below in Scheme 10.

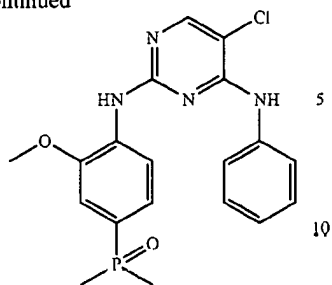
Scheme 10



In a non limiting example, Schemes 10A and 10B illustrate the preparation of compounds of Formula VIA in which L is NH and Ring A and Ring E are substituted phenyl:

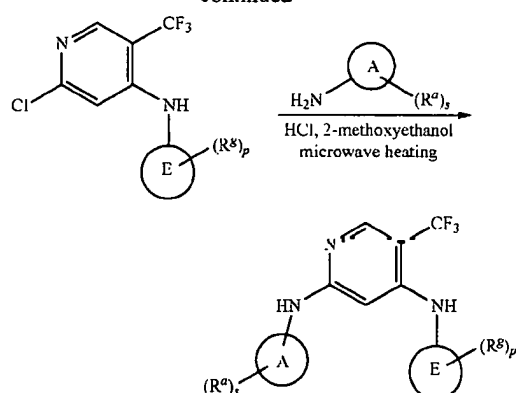
Scheme 10A



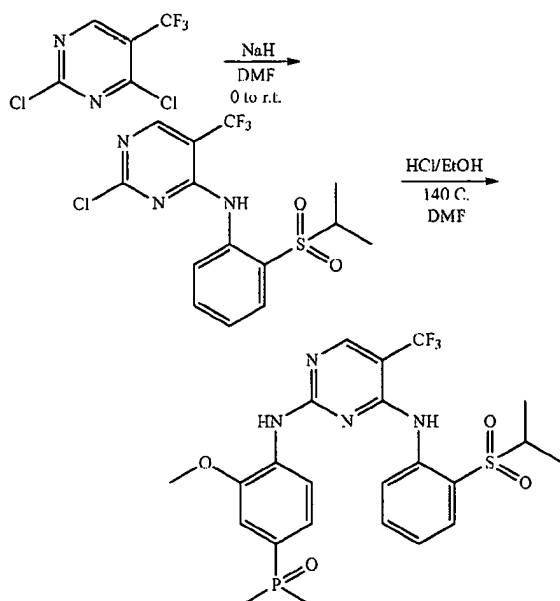
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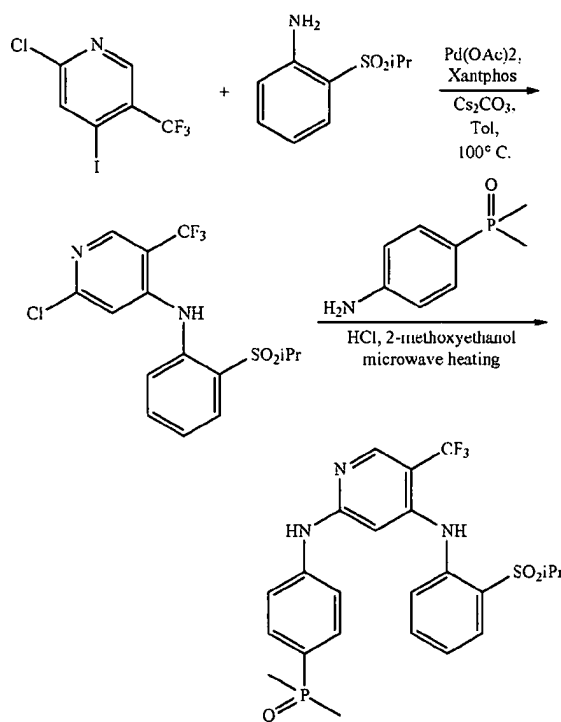


Scheme 10B



In a non limiting example, Scheme 11A illustrates the preparation of compounds of Formula VIA in which L is NH, X¹ is CH, and Ring A and Ring E are substituted phenyl.

Scheme 11A



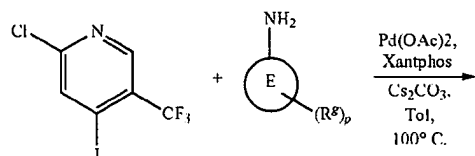
The synthetic guidance provided in Schemes 1 through 10 is applicable to a variety of Ring A and Ring E of the invention and allows the preparation of all compounds of the invention.

Scheme 11 illustrates the preparation of a compound of Formula IA and VIA in which n is 0, L is NH and X¹ is CH.

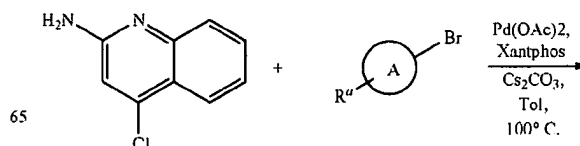
In Scheme 11, [Ring E]-NH moiety is incorporated onto the pyridine central scaffold by reacting 2-chloro-4-iodo-5-(trifluoromethyl)pyridine with [Ring E]-NH₂ using Palladium coupling reaction conditions. [Ring A]-NH moiety is then incorporated by displacement chemistry as previously described in the above Schemes. Microwaves and heat can also be used to accelerate or drive the displacement reaction to completion.

Scheme 12 illustrates the synthesis of a compound of Formula IVA in which X¹ is CH and R^d and R^e form a phenyl ring.

Scheme 11

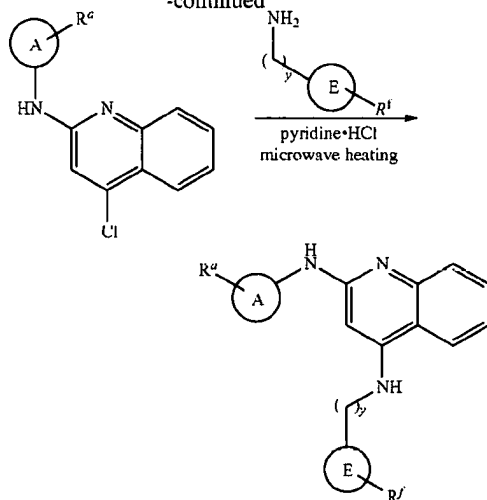


Scheme 12



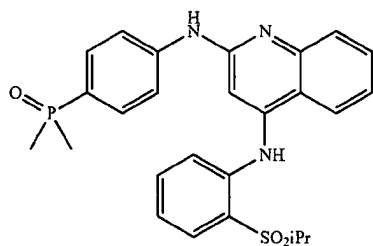
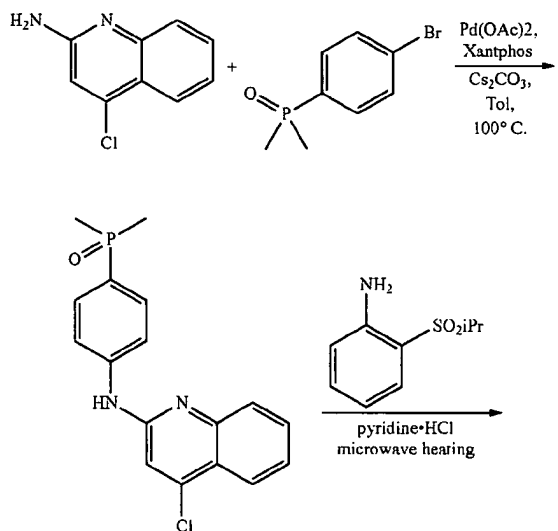
105

-continued



In a non limiting example, Scheme 12A illustrates the preparation of compounds of Formula IVA in which X¹ is CH and R^d and R^e form a phenyl ring, Ring A and Ring E are substituted phenyl.

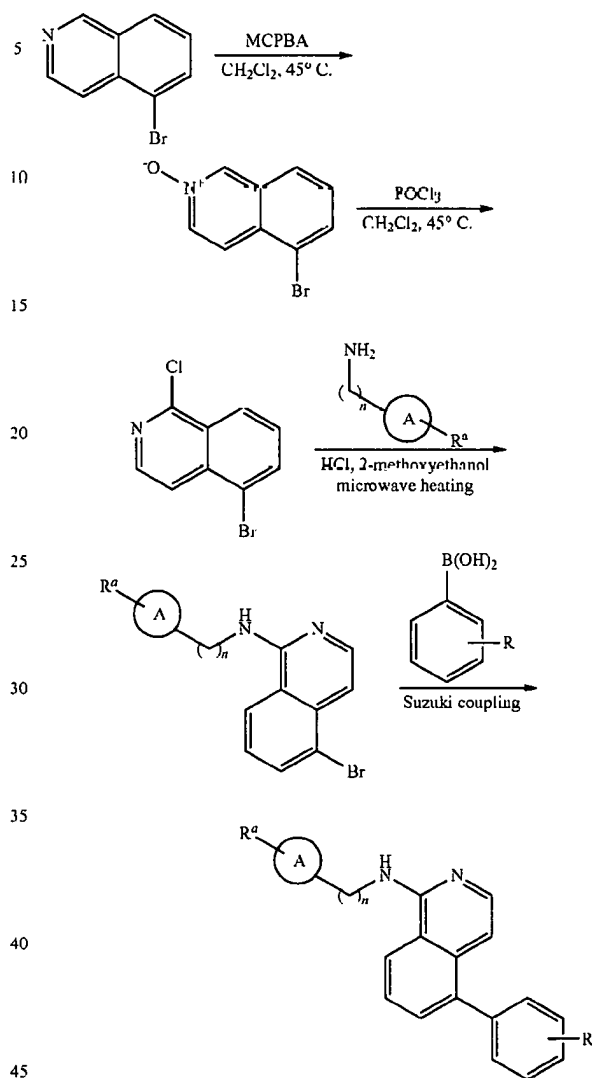
Scheme 12A



Scheme 13 illustrates the synthesis of a compound of Formula IIIA in which X¹ is CH and R^b and R^c form a phenyl ring which is further substituted with a phenyl ring.

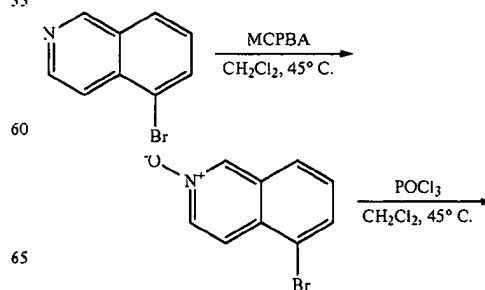
106

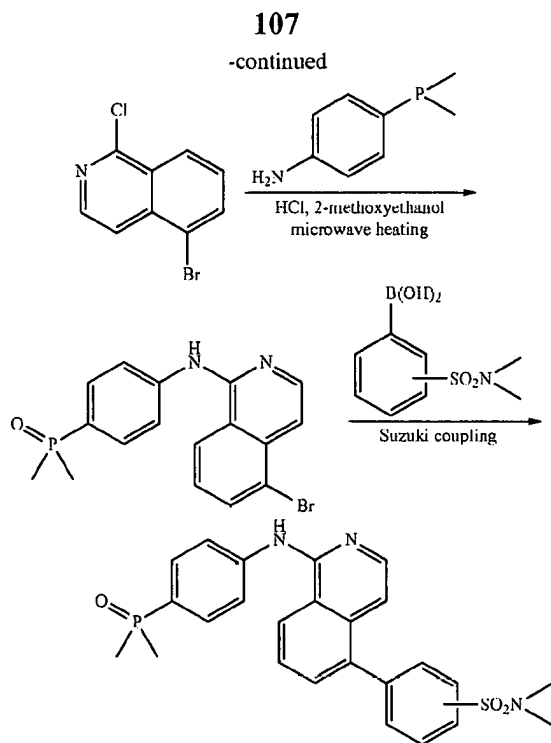
Scheme 13



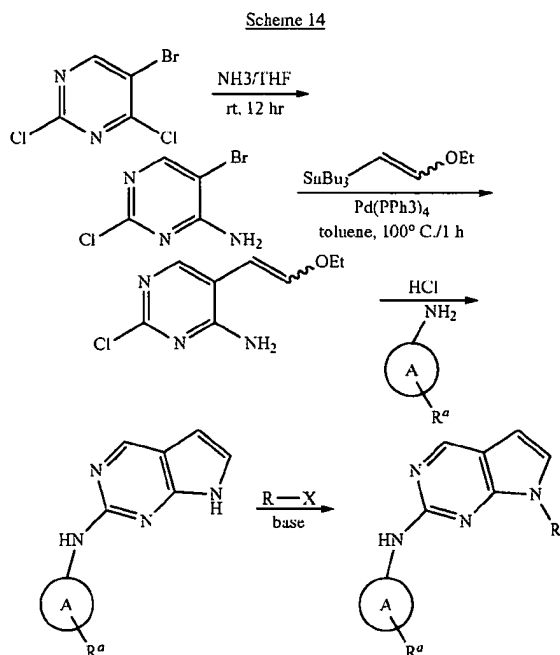
In a non limiting example, Scheme 13A illustrates the preparation of compounds of Formula VA in which X¹ is CH and R^b and R^c form a phenyl ring, Ring A is substituted phenyl and R^f is a substituted phenyl.

Scheme 13A



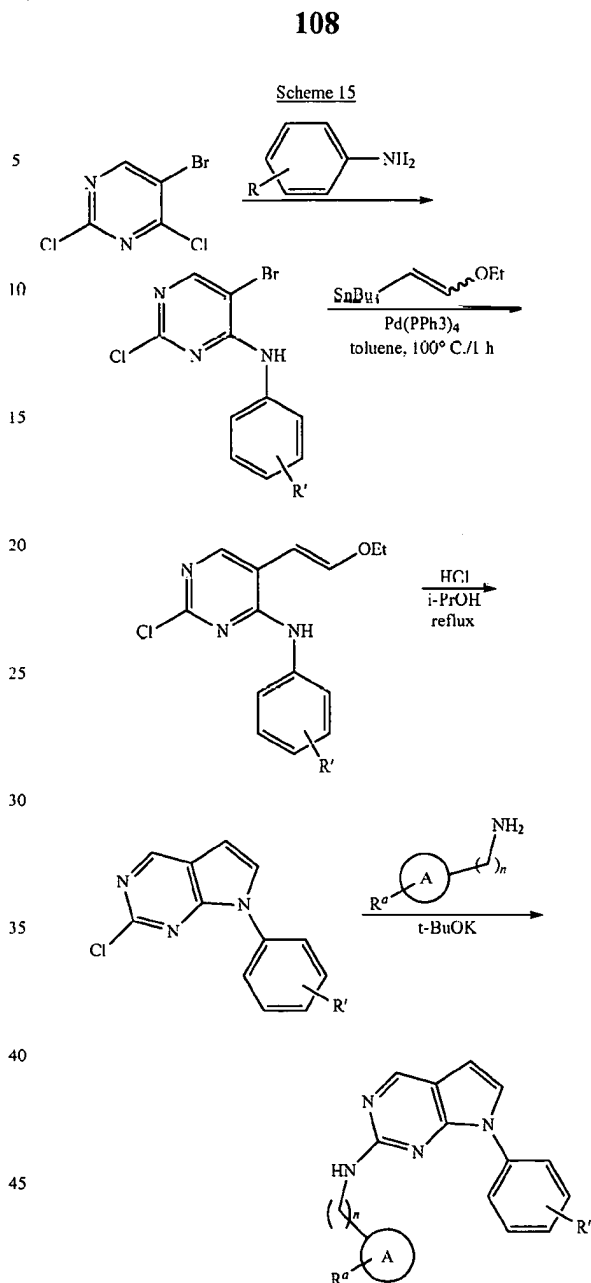


Scheme 14 illustrates the synthesis of a compound of Formula IIIA in which X^1 is N and R^c and R^d form a pyrrole.



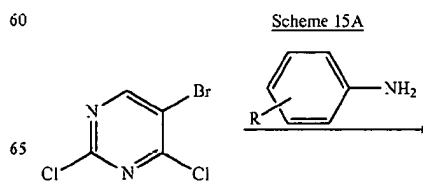
in which Ring A and R^a are as defined in part 1 and in $R-X$, R is alkyl, heteroaryl, aryl, aryl alkyl, heteroaryl alkyl, heterocycl and other groups selected from the R' list of substituents; and X is a halide or other leaving groups.

Another example of preparation of a compound of Formula IIIA is illustrated below in Scheme 15 in which substituent R depicted in scheme 14 is a phenyl.



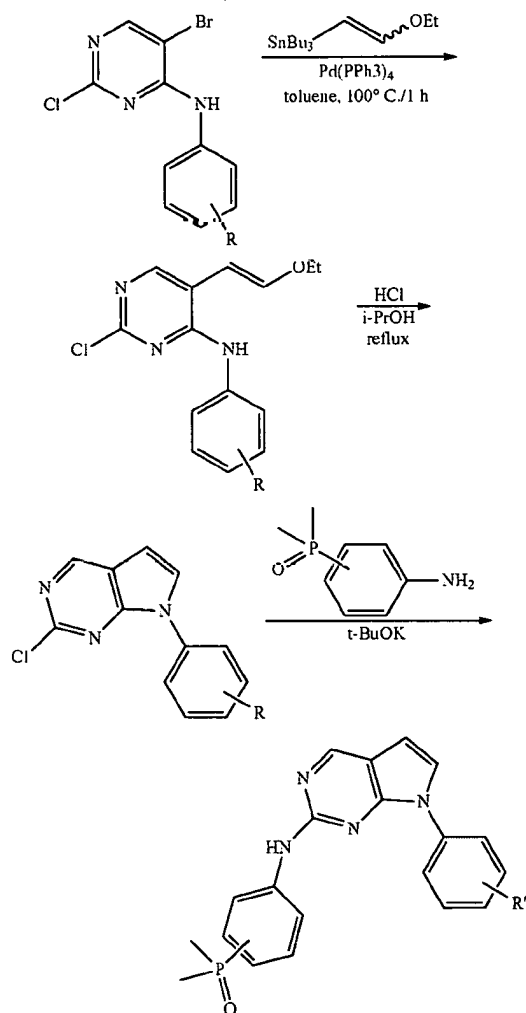
in which R' is a substituent selected from R' list and Ring A and R^a are defined in part 1.

In a non limiting example, Scheme 15A illustrates the preparation of compounds of Formula IIIA in which X^1 is N, R^c and R^d form a pyrrole, Ring A is a substituted phenyl and R' is a substituted phenyl:



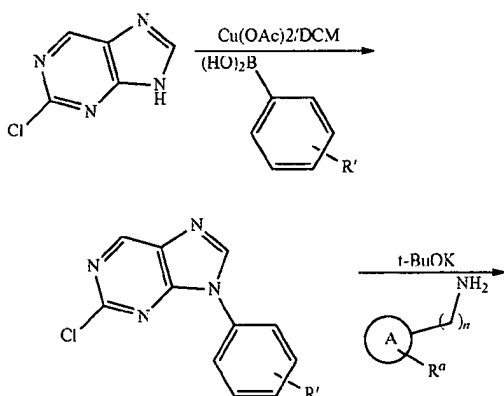
109

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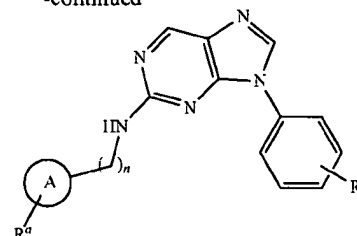
In a non limiting example, Scheme 16 illustrates the preparation of compounds of Formula IIIA in which X^1 is N and R^c and R^d form an imidazole ring which is substituted with a phenyl.

Scheme 16



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-continued



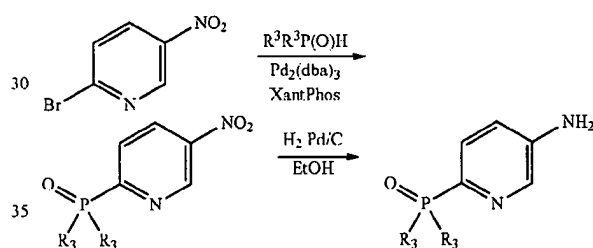
in which R^1 is a substituent selected from R^f list and Ring A and R^a are defined in part 1.

For the compounds of the invention, one of R^a , R^b , R^{b1} , R^c , R^{c1} , R^d , R^{d1} , R^e , R^{e1} , R^f or R^g when present, is or contains $-P(=O)(R^3)_2$.

Schemes 17 to 24 illustrate the preparation of phosphorous containing substituents and phosphorous containing moieties of current interest.

Scheme 17 illustrates the preparation of a [Ring A]- NH_2 moiety in which Ring A is a pyridine substituted with $-P(=O)(R^3)_2$.

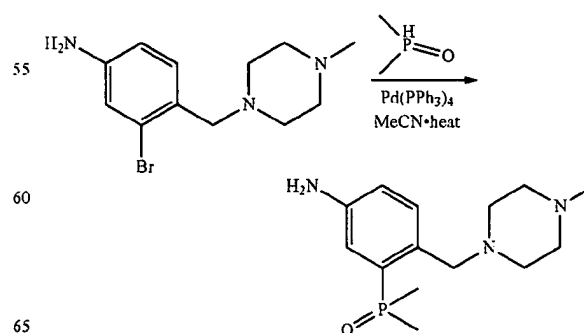
Scheme 17



in which R^3 is defined in part 1. A similar synthetic route could be used to introduce a $-P(=O)(R^3)_2$ substituent onto a phenyl or heteroaryl ring whether the ring is Ring A or Ring E. This synthetic scheme also illustrates the preparation of a [Ring E]-L moiety in which L is NH and Ring E is aryl or heteroaryl. This scheme can be used for the synthesis of compounds of the invention of Formulae I to VI.

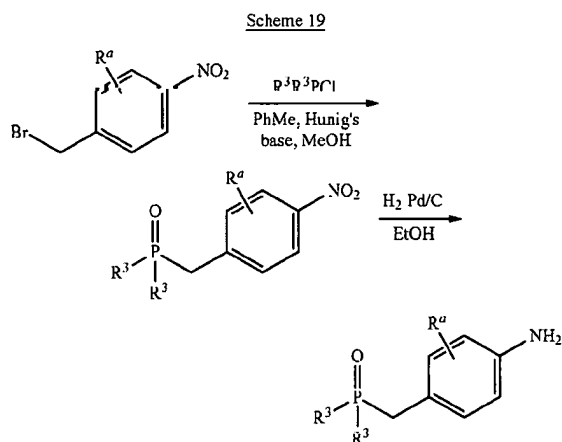
Of other interest are compounds in which R^a substituent is phosphorous containing substituent. Scheme 18 illustrates the synthesis of an intermediate [Ring A]- NH_2 in which Ring A is a phenyl substituted with $-P(=O)(CH_3)_2$.

Scheme 18



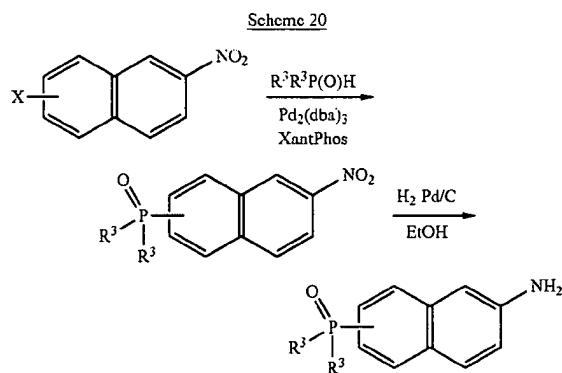
111

Scheme 19 illustrates the preparation of a [Ring A]-NH₂ intermediate in which Ring A is a phenyl substituted with (CH₂)_m-P(=O)(R³)₂ and m is 1. This scheme is useful for the synthesis of compounds of Formulae II and IIA.

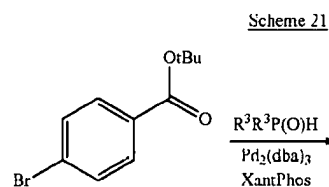


Scheme 20 illustrates the preparation of a [Ring A]-NH₂ moiety in which Ring A is a bicyclic structure such as naphthalene substituted with R⁷ being -P(=O)(R³)₂.

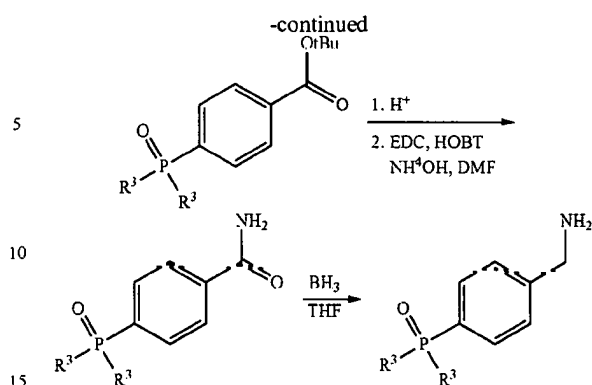
This scheme could also be used to prepare a [Ring E]-L moiety in which Ring E is naphthalene, L is NH and R⁸ is -P(=O)(R³)₂. This scheme can also be used for the synthesis of compounds of the invention of Formulae VIIA.



Scheme 21 illustrates the synthesis of [Ring A]-(CH₂)_n-NH₂ intermediate in which Ring A is phenyl substituted with -P(=O)(R³)₂ and n is 1.



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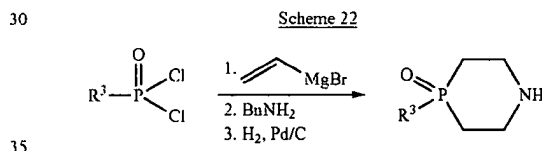


Scheme 21 can also be used for the synthesis of a [Ring F]-I moiety in which L is CH₂NH and Ring E is a phenyl substituted with -P(=O)(R³)₂.

In some embodiment, a R^a, R⁷ or R⁸ containing -P(=O)(R³)₂ substituent can be of cyclic structure.

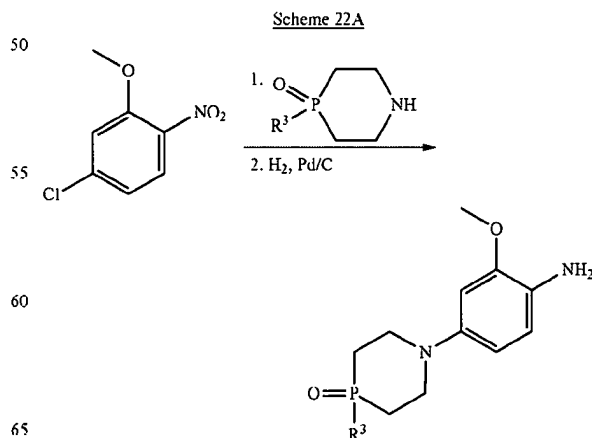
Schemes 22 to 23 illustrate the synthesis of cyclic structures of interest containing -P(=O)(R³)₂.

Scheme 22 illustrates the preparation of cyclic substituent R^a (or R⁷ or R⁸) containing -P(=O)(R³)₂.



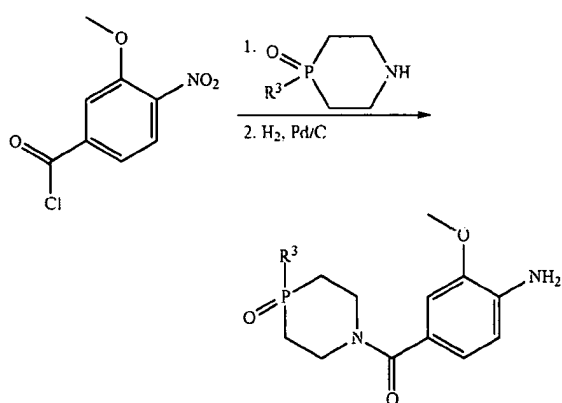
Schemes 22A and 22B illustrate the incorporation of this cyclic substituent onto a Ring A or Ring E.

Scheme 22A illustrates the synthesis of a [Ring A]-NH₂ moiety in which Ring A is a phenyl substituted with a methoxy group and with a -P(=O)(R³)₂ containing cyclic substituent. This scheme could also be used for the synthesis of a [Ring E]-L moiety in which L is NH and Ring E is a phenyl substituted with a methoxy group and with a -P(=O)(R³)₂ containing cyclic substituent.



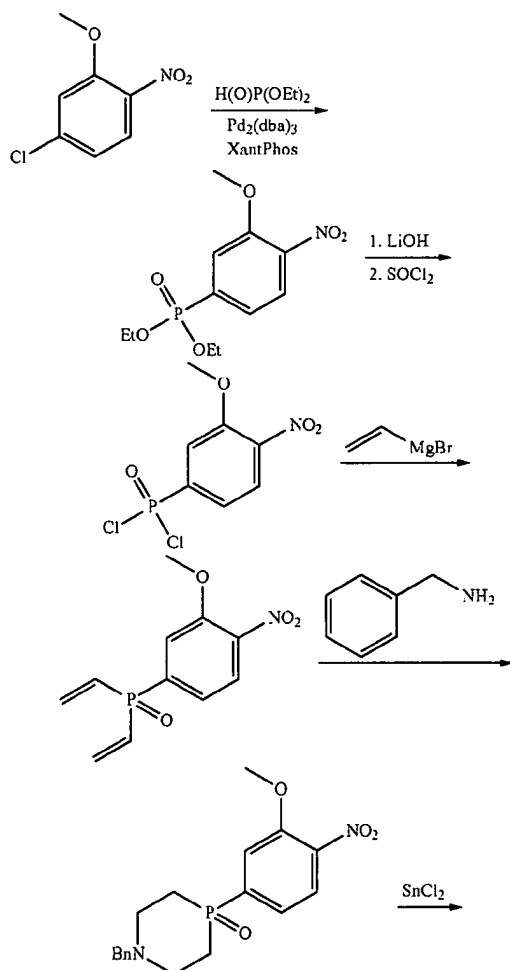
113

Scheme 22B



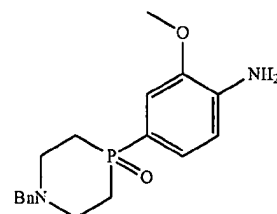
Scheme 23 illustrates the synthesis of a [Ring A]-NH₂ intermediate in which Ring A is phenyl substituted by methoxy and a —P(=O)(R³)₂ group in which the two R³ groups form with the phosphorous atom to which they are attached 6-membered saturated ring.

Scheme 23



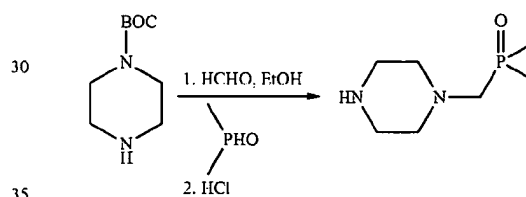
114

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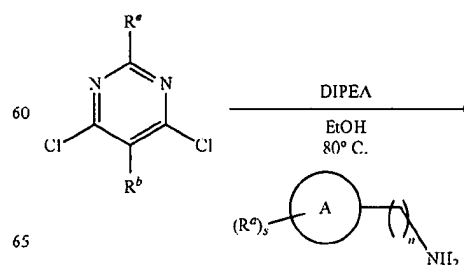
Scheme 24 illustrates the synthesis of a piperazine substituent which is further substituted with —CH₂P(=O)(CH₃)₂. This scheme can be used for the synthesis of [Ring A]-NH₂ intermediate in which Ring A is a phenyl substituted with a phosphorous containing piperazine group. It could also be used for the synthesis of a compound of any of the Formulae of the invention in which one of the substituents (R^a, R^b, R^c, R^d, R^e, R^f or R^g) is NR¹R² and NR¹R² form a piperazine ring substituted with —CH₂P(=O)(CH₃)₂.

Scheme 24



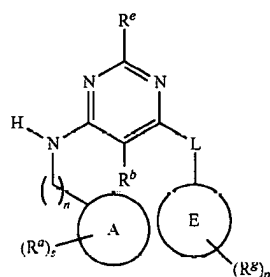
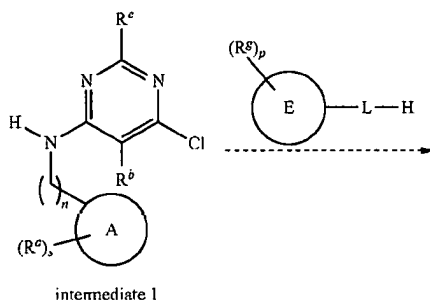
A compound of Formula IB or VI can be prepared in a 2 steps synthesis as shown in Scheme 1. A [Ring A] moiety can first be incorporated to the central pyrimidine moiety by reacting [Ring A]-NH₂ with a substituted or unsubstituted 4,6-dichloropyrimidine in the presence of a base such as di-isopropylethyl amine at high temperature generating intermediate 1a. The [Ring E]-L-moiety can then be incorporated onto intermediate 1a using various conditions depending on the nature of the L linker. The variables in the intermediate [Ring E]-[L]- and [Ring A] are as defined previously, Rings A and E being substituted with permitted R^a and R^a groups respectively.

Scheme 25

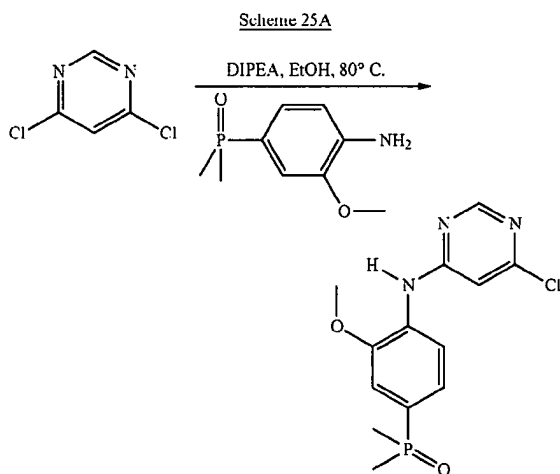


115

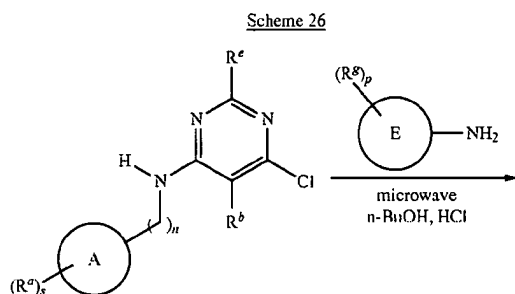
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An approach to the preparation of an intermediate 1a is illustrated below in Scheme 1A in which Ring A is a phenyl:

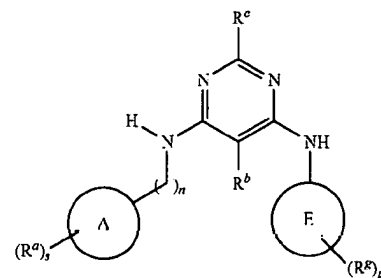


A compound of Formula IB or VII in which L is NH can be prepared using microwave chemistry, by reacting an intermediate 1a with [Ring E]-NH₂ in a solvent such as n-Butanol under acidic conditions as shown in Scheme 26.

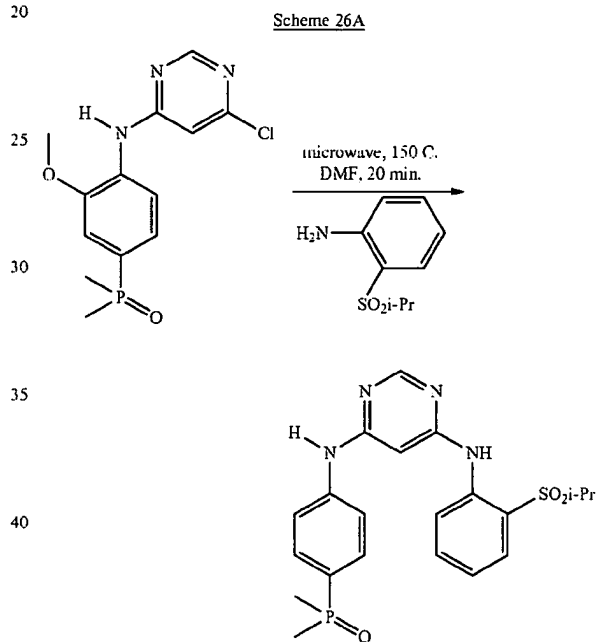


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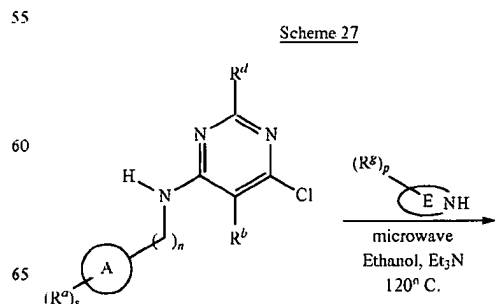
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15 An approach to the preparation of a compound of Formula VI in which L is NH, is illustrated below in Scheme 26A in which Ring A and Ring E are phenyls:

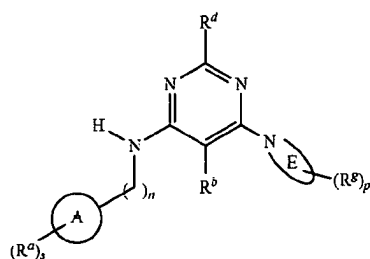


A compound of Formula IB or VII in which L is bond and [Ring E] is a N-linked heterocyclyl, can be prepared by reacting an intermediate 1a with the heterocyclyl, in the presence of a base such as di-isopropyldiethylamine, in a polar solvent such as iso-propanol, and using high temperatures, as shown in Scheme 27:



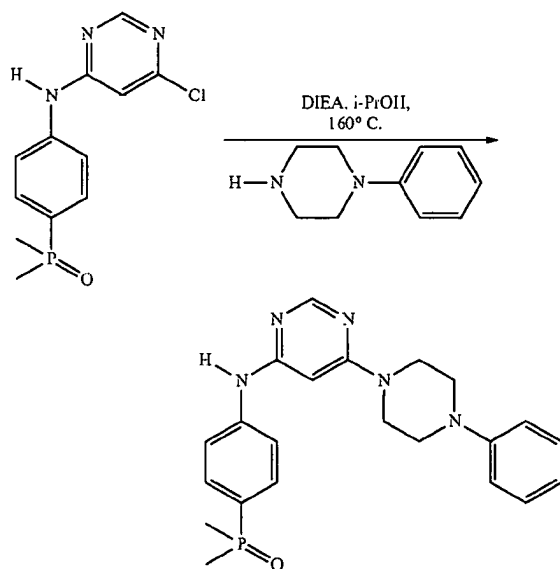
117

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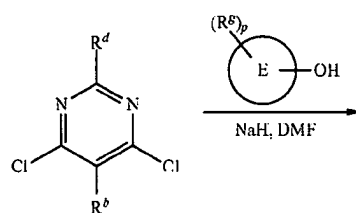
In a non limiting example, Scheme 27A illustrates the preparation of a compound of Formula VII or IB in which R^c is [L]-[Ring E] in which L is a bond and [Ring E] is N-phenyl-piperazine.

Scheme 27A



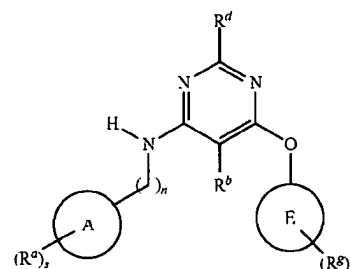
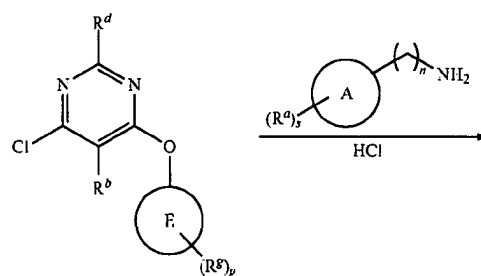
A compound of Formula IB or VII in which R^c is [L]-[Ring E] with L being O can be prepared by reacting 4,6-dichloropyrimidine with an optionally substituted phenol; in the presence of sodium hydride in a solvent such as dimethylformamide as shown in Scheme 28. A [Ring A] moiety can then be incorporated to the central pyrimidine moiety by reacting [Ring A]-(CH₂)_nNH₂ in the presence of a base (i.e. di-isopropylethyl amine, triethylamine or the like) or an acid in order to facilitate the displacement reaction.

Scheme 28



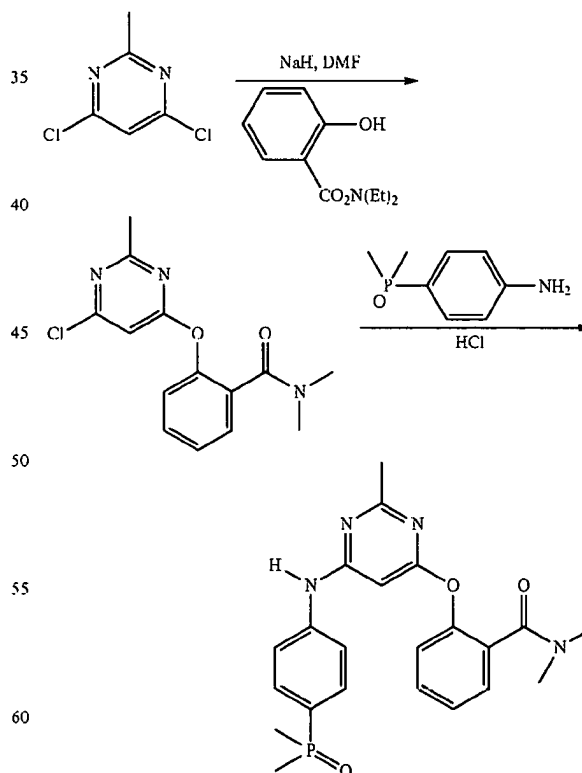
118

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An approach to the preparation of a few compounds of Formula IB or VII in which L is NH, is illustrated below in Scheme 28A in which Ring A and Ring E are phenyls:

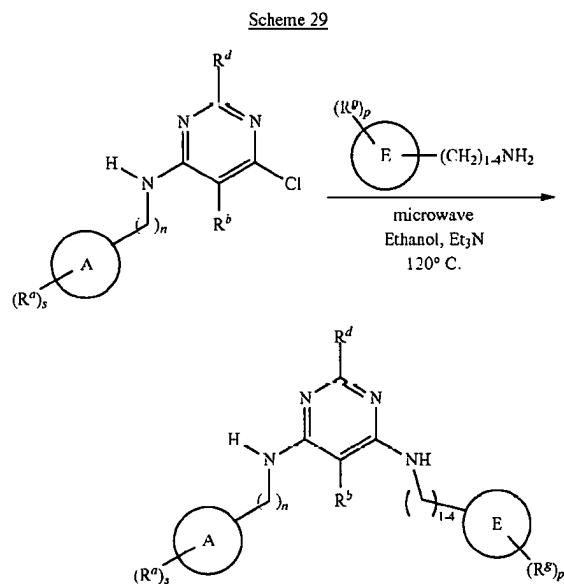
Scheme 28A



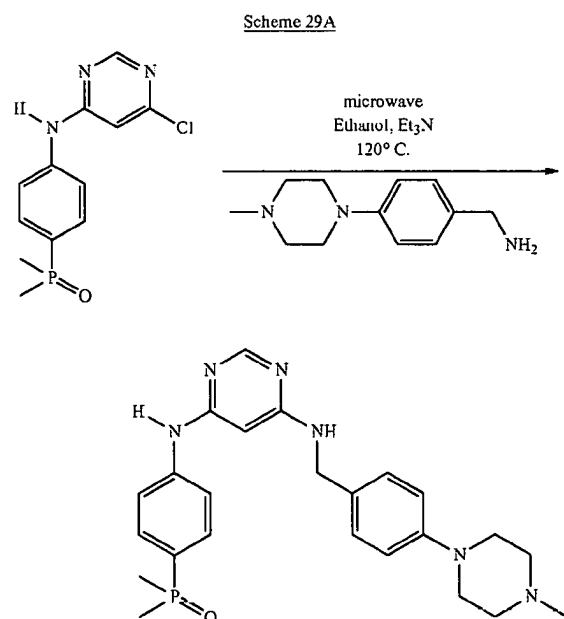
A compound of Formula IB or VII in which L is NH(CH₂)₁₋₄ can be prepared using microwave chemistry, by reaction an intermediate 1a with [Ring E]-(CH₂)₁₋₄NH₂, in

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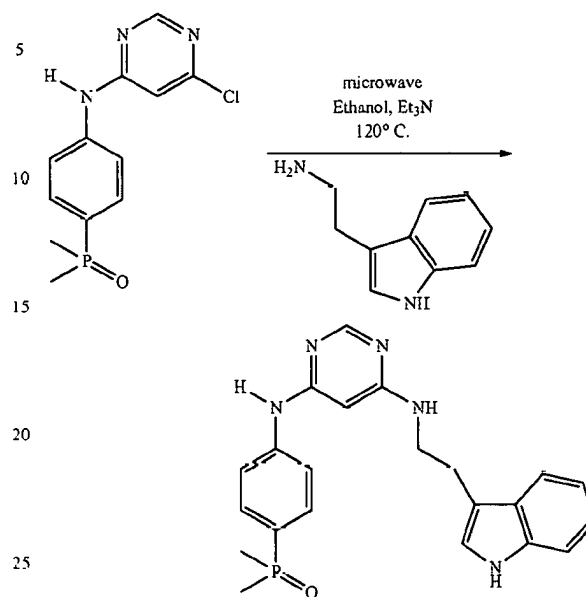
the presence of a base such as triethylamine, in a polar solvent such as Ethanol, and using high temperatures, as shown in Scheme 29:



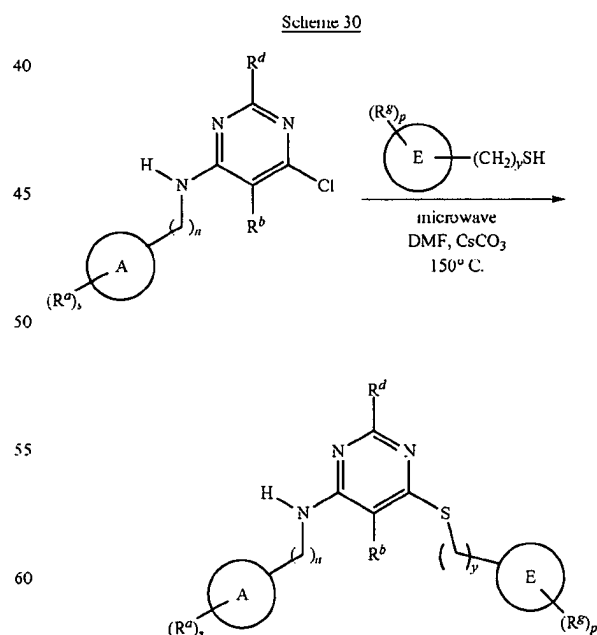
An approach to the preparation of a few compounds of Formula VII in which L is NH(CH₂)₁₋₄, is illustrated below in Schemes 29A and 29B. Scheme 29A illustrates the synthesis of a compound of Formula VII in which Ring E is a phenyl and L is NHCH₂ and Scheme 29B illustrates the synthesis of a compound of Formula VII in which Ring E is 3-1H-indole and L is NH(CH₂)₂:



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Scheme 29B

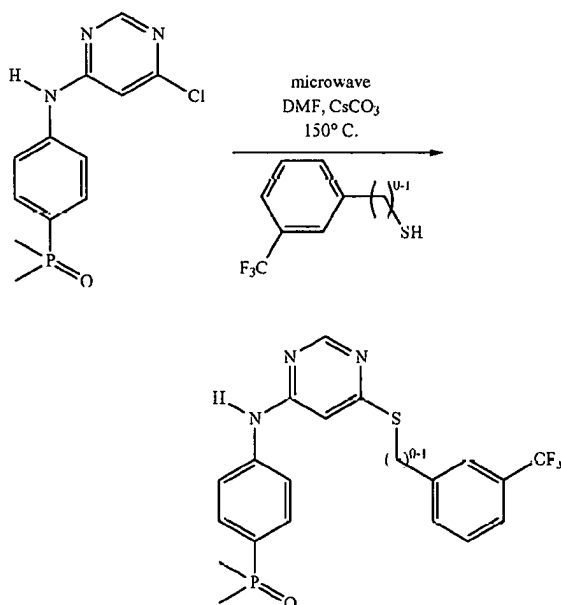
A compound of Formula IB and VII in which L is SH(CH₂)_y can be prepared using microwave chemistry, by reaction an intermediate 1a with [Ring E]-(CH₂)_ySH, in the presence of a base such as Cesium carbonate, and in a solvent such as dimethylformamide at high temperatures, as shown in Scheme 30. The variable y is defined above.



An approach to the preparation of a compound of Formula VII in which X³ is CH, X² is N, L is S(CH₂)_y, and Rings A and E are substituted phenyls, is illustrated below in Scheme 30A:

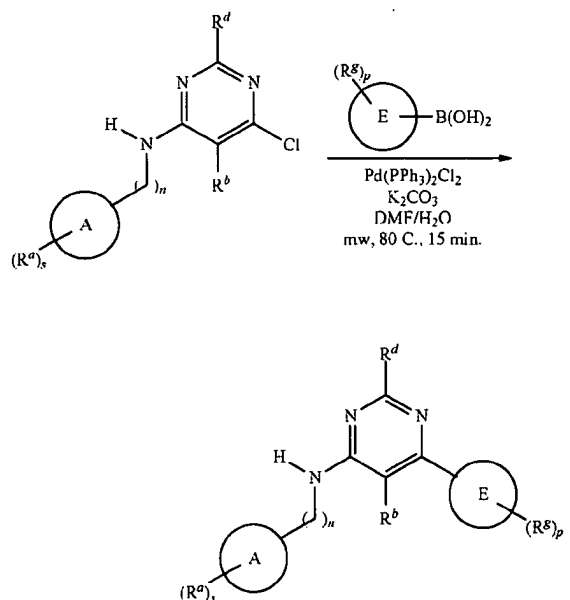
121

Scheme 30A



A compound of Formula IB or VII in which L is bond and [Ring E] is an aryl or heteroaryl, can be prepared using Suzuki coupling conditions. Scheme 31 illustrates the Suzuki coupling reaction.

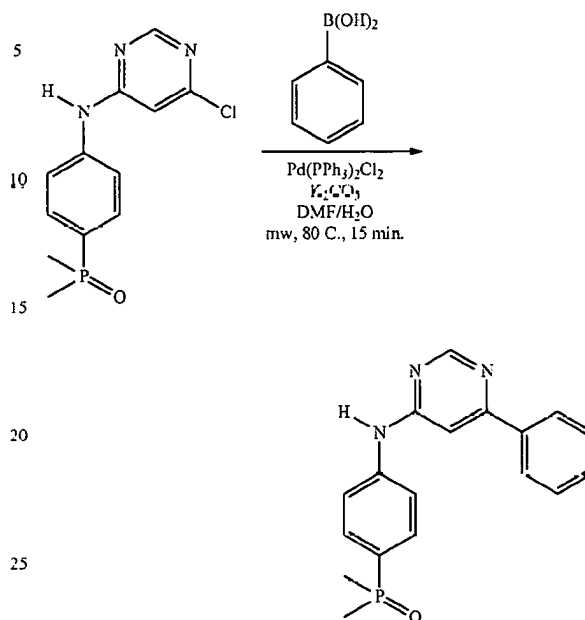
Scheme 31



In a non limiting example, Scheme 31A illustrates the preparation of a compound of Formula VII in which X² is CH, X² is N, L is a bond and [Ring E] and [Ring A] are phenyl.

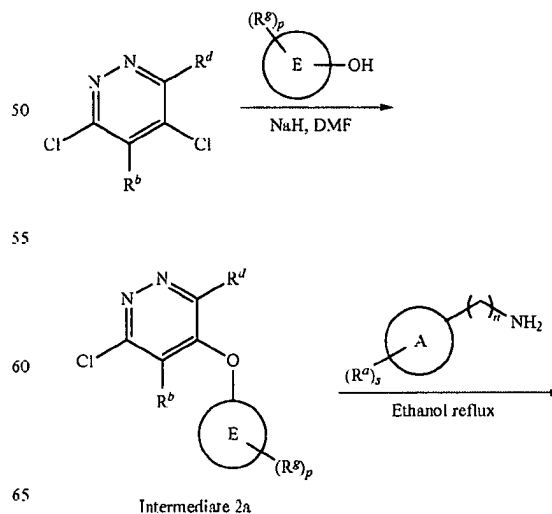
122

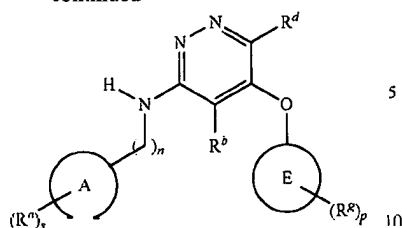
Scheme 31A



A compound of Formula IC or VI in which R^c is [L]-[Ring E] with L being O, can be prepared in a 2 steps synthesis as shown in Scheme 32. A [Ring E]-L-moiety can first be incorporated to the central pyridazine moiety by reacting [Ring E]-OH with a substituted or unsubstituted 3,5-dichloropyridazine in the presence of a base such as sodium hydride generating intermediate 2a. The [Ring A]-(CH₂)_nNH₂ moiety can then be reacted with intermediate 2a in the presence of a base (i.e. di-isopropylethyl amine, triethylamine or the like) or an acid in order to facilitate the displacement reaction.

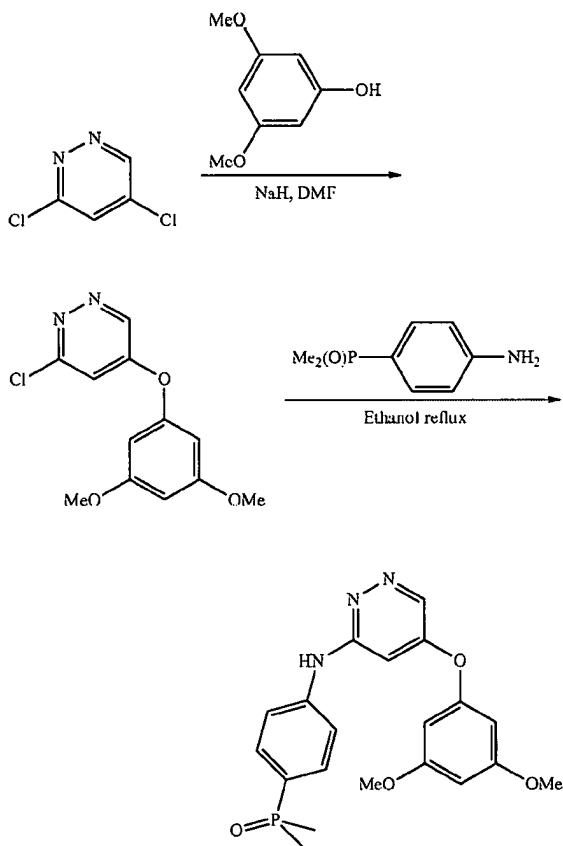
Scheme 32



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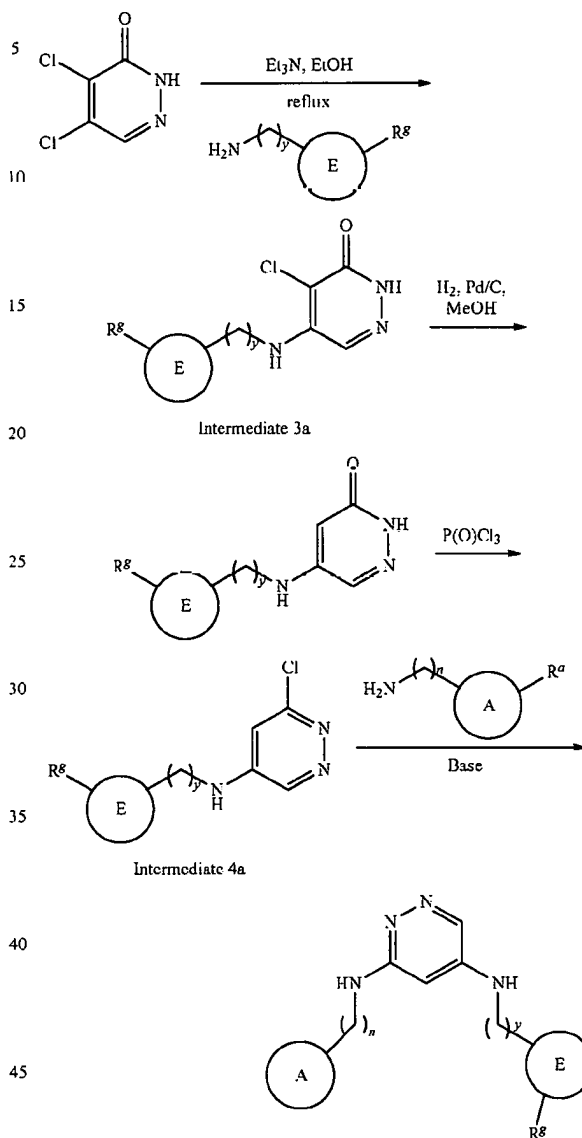
In a non limiting example, Scheme 32A illustrates the preparation of a compound of Formula VII in which L is O, X³ is N, X² is CH and [Ring E] and [Ring A] are substituted phenyl.

Scheme 32A



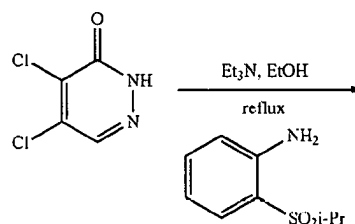
124

Scheme 33



In a non limiting example, Scheme 33A illustrates the preparation of a compound of Formula VII in which L is NH, X³ is N, X² is Cl and [Ring E] and [Ring A] are substituted phenyl.

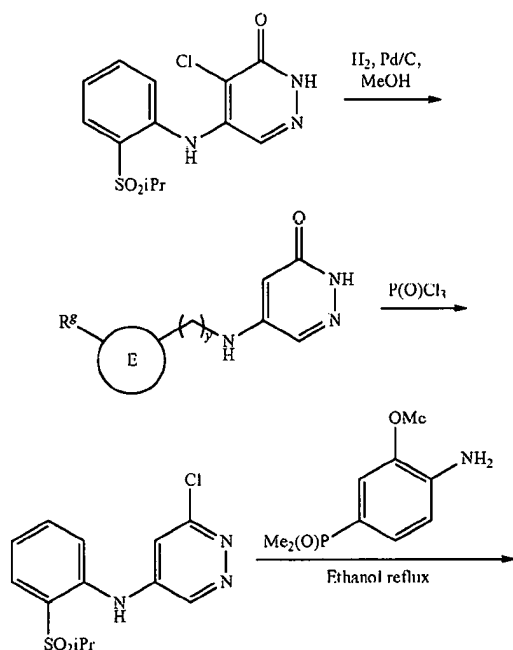
Scheme 33A



A compound of Formula IC in which R^c is [L]-[Ring E] with L being NH(CH₂)_y, can be prepared in 4 steps as shown in Scheme 33. A [Ring E](CH₂)_y-NH₂ moiety can first be incorporated to the central pyridazine moiety by reacting [Ring E]-(CH₂)_y-NH₂ with 4,5-dichloropyridazin-3(2H)-one in the presence of triethylamine in a solvent such as Ethanol generating intermediate 3a. Intermediate 3a is then hydrogenated and reduced with phosphoric trichloride generating intermediate 4a. The [Ring A]-(CH₂)_n-NH₂ moiety can then be reacted with intermediate 4a in the presence of a base (i.e. di-isopropylethyl amine, triethylamine or the like) or an acid in order to facilitate the displacement reaction.

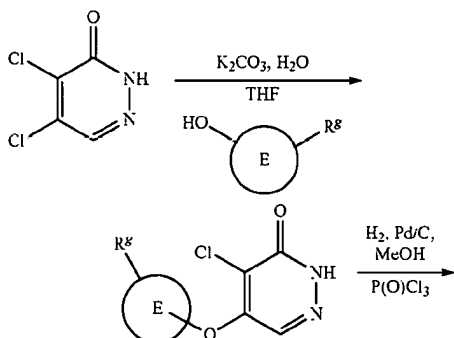
125

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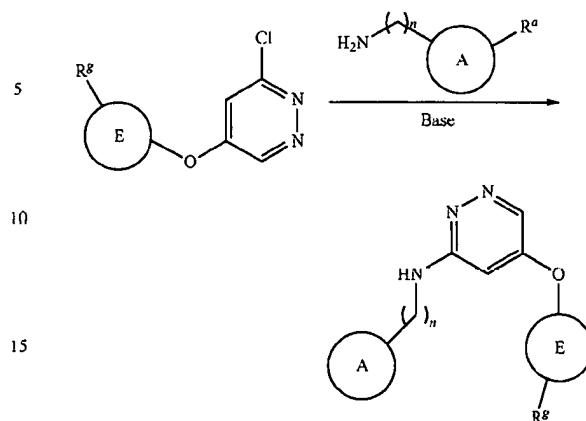
In a similar way, a compound of Formula IC or VI in which R^c is [L]-[Ring E] with L being O, can be prepared by reacting [Ring E]-OH with 4,5-dichloropyridazin-3(2H)-one in the presence of potassium carbonate; followed by the same sequence of steps as described in Scheme 33. This alternative synthesis is illustrated in Scheme 34:

Scheme 34



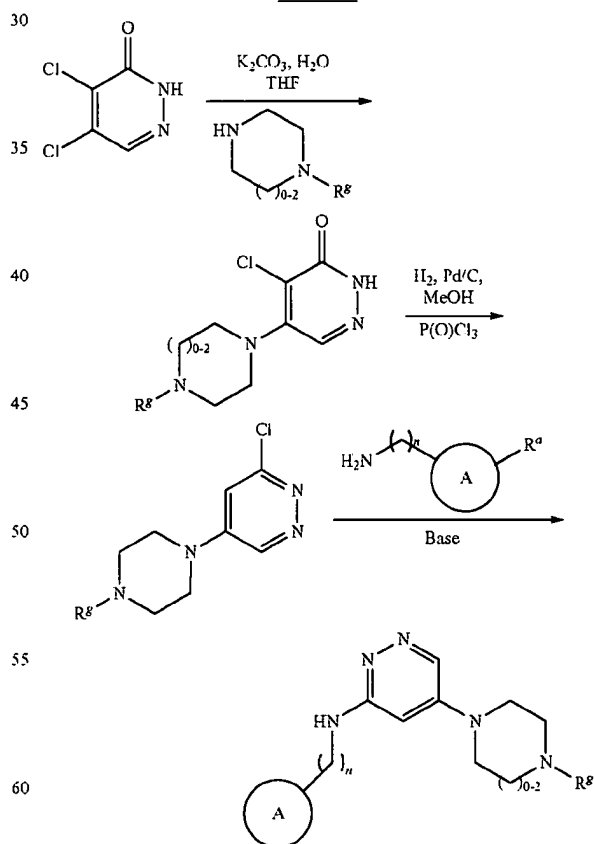
126

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In a similar way, a compound of Formula IC in which R^c is a N-linked heterocyclyl can be prepared by reacting a heterocyclyl such as a substituted piperidine with 4,5-dichloropyridazin-3(2H)-one followed by the same sequence of steps as described in Scheme 9. This synthesis is illustrated in Scheme 35:

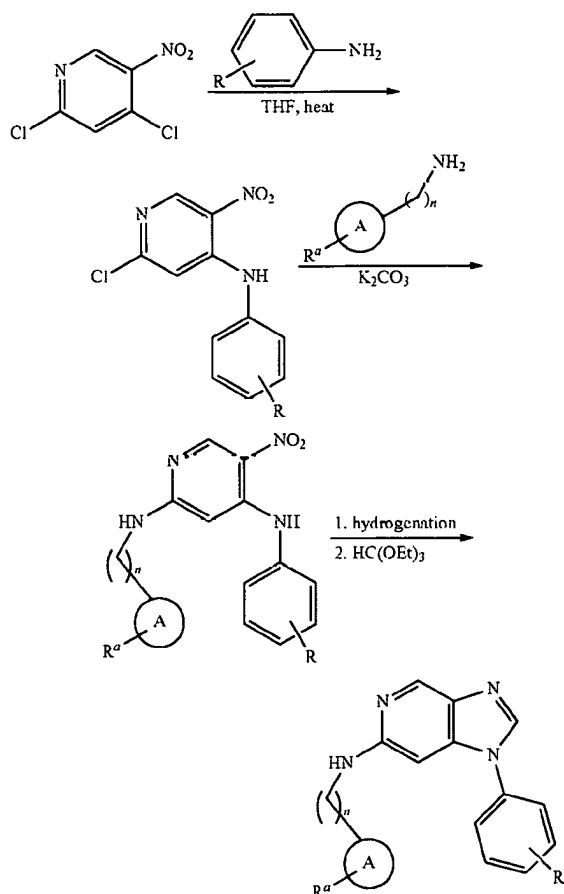
Scheme 35



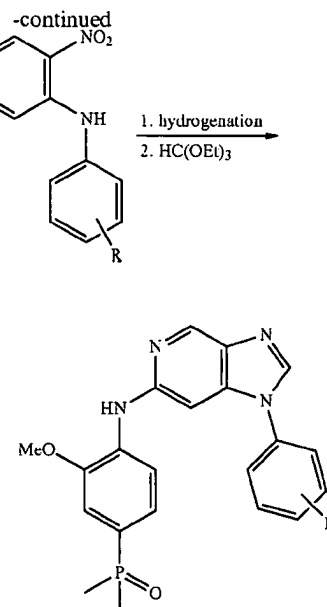
Scheme 36 illustrates the synthesis of a compound of Formula IIIA in which R^c and R^d are H and R^c and R^d form an imidazole substituted with a phenyl group.

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Scheme 36



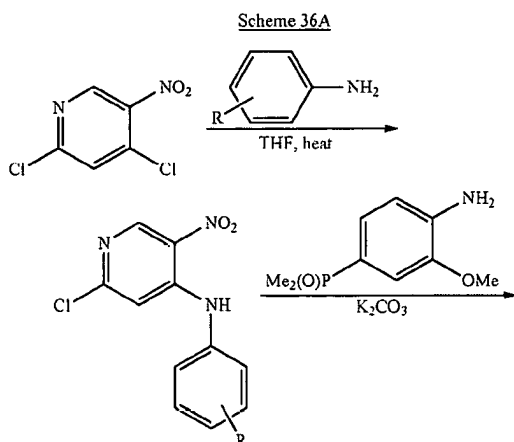
128



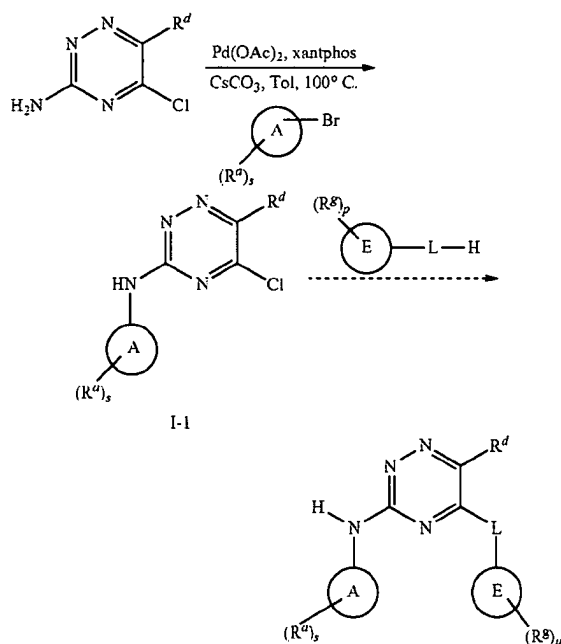
A compound of Formula I, IB, IIB or VIA in which n is 0 can be prepared in a 2 steps synthesis as shown in Scheme 37. A [Ring A] moiety can first be incorporated to the central triazine moiety by reacting [Ring A]-Br with 5-chloro-6-substituted-1,2,4-triazin-3-amine under Buchwald Hartwig cross coupling conditions to generate intermediate 1 (I-1). The [Ring E]-L-moiety can then be incorporated onto I-1 using various conditions depending on the nature of the L linker. The variables in the intermediate [Ring E]-[L]- and [Ring A] are as defined previously, Rings A and E being substituted with permitted R^a and R^g groups respectively.

in which R is a substituent selected from R^f and Ring A, R^a and n are defined above.

In a non limiting example, Scheme 36A illustrates the preparation of compounds of Formula IIIA in which R^c and R^d form an imidazole, Ring A is a substituted phenyl and R^f is a substituted phenyl:

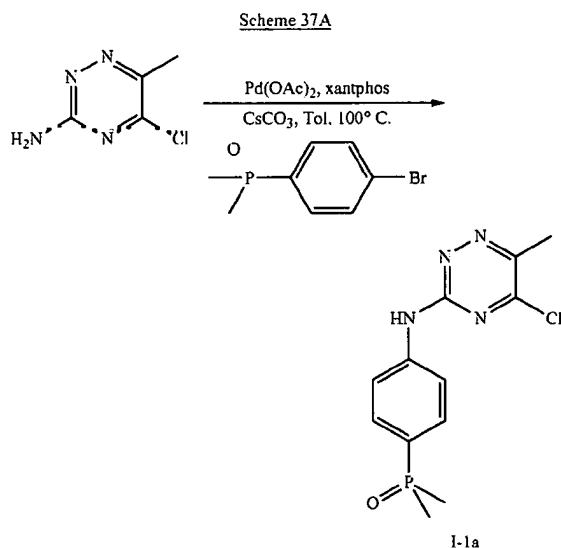


Scheme 37

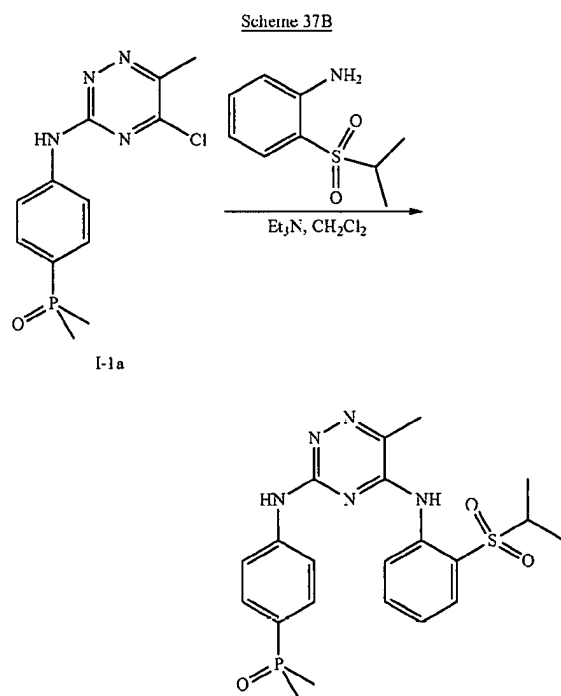


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An approach to the preparation of an intermediate 1c is illustrated below in Scheme 37A in which Ring A is a phenyl:



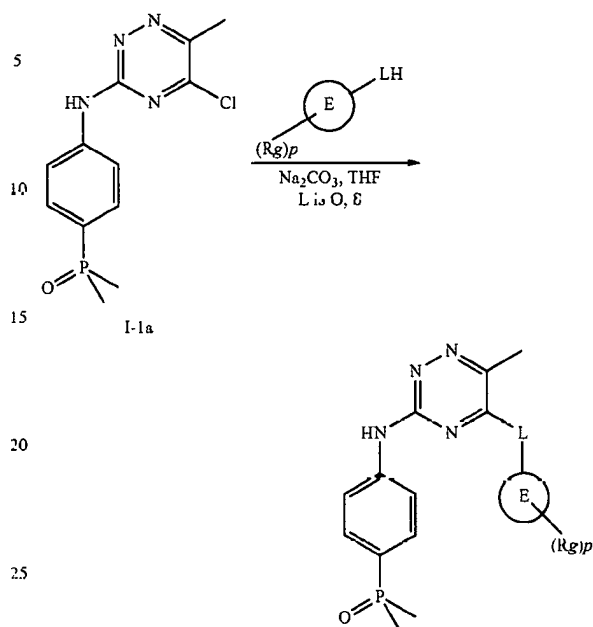
Intermediate I-1a is then reacted with a substituted aniline, as illustrated in Scheme 37B, to generate compound of Formula VIA in which L is NH, Ring A and Ring E are phenyl, n is 0, and R^d is methyl.



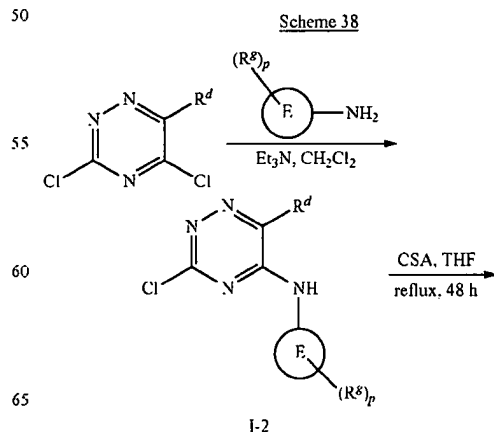
Intermediate I-1a can also be reacted with a substituted phenol or thiophenol, as illustrated in Scheme 37C, to generate compound of Formula VIA in which L is O or S, Ring A and Ring E are phenyl, n is 0, and R^d is methyl.

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Scheme 37C

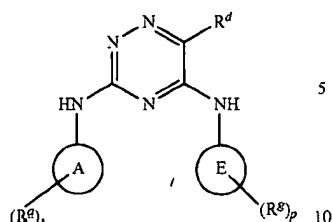


An alternative synthesis to compounds of Formula I, IB, IIB or VIA is illustrated in Scheme 38. [Ring E]-LH moiety, in which L is O, S or NH, can be first incorporated to the central triazine moiety prior to the incorporation of [Ring A]-NH moiety. Schemes 38 and 39 illustrates the reaction of 3,5-dichloro-6-substituted-1,2,4-triazine with a [Ring-E]-LH moiety in the presence of a base (for example triethylamine, potassium carbonate, sodium carbonate or sodium hydride or the like) in a suitable solvent such as for example dimethylformamide, methylene chloride or tetrahydrofuran in order to generate intermediate I-2 and I-3. The reaction can be performed at room temperature or may require higher temperature. Intermediates I-2 and I-3 are then reacted with a [Ring A]-NH₂ moiety under acidic conditions (i.e. Camphor sulfonic acid) in the presence of a suitable solvent such as for example tetrahydrofuran at high temperature. This sequence of reactions is described in PCT application WO 2006/015985.

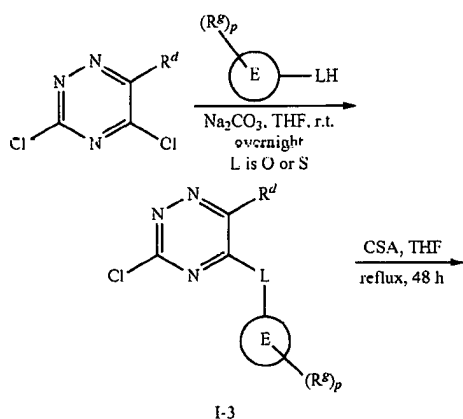


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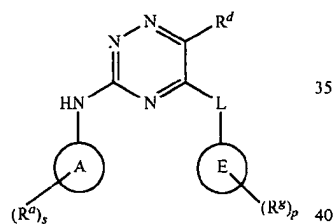
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Scheme 39

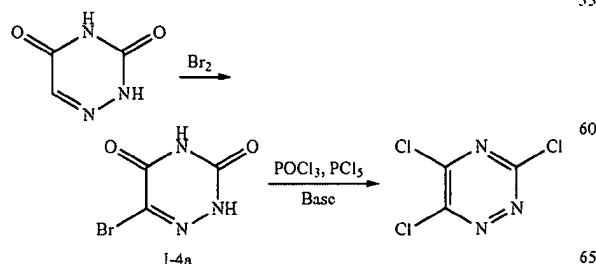


I-3



When R^d is chloro, 3,5,6-trichloro-1,2,4-triazine, can be prepared according to methods described in PCT patent application WO 2004/074266, by reacting 1,2,4-triazine-3,5 (2H, 4H)dione with bromine in a presence of a suitable solvent, such as for example water, to generate an intermediate of Formula I-4a. Synthesis of 3,5,6-trichloro-1,2,4-triazine is illustrated in Scheme 40. Intermediate I-4a is then reacted with POCl_3 and PCl_5 in the presence of a base such as for example N,N-diethylaniline.

Scheme 40



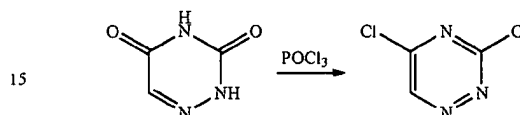
I-4a

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When R^d is Methyl, 3,5-dichloro-6-methyl-1,2,4-triazine can be prepared according to methods described in PCT patent application WO 2005/054199.

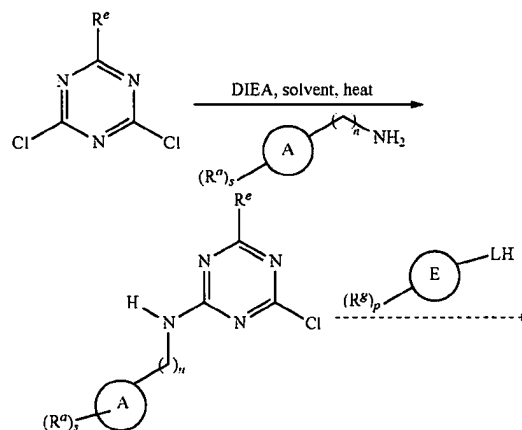
When R^d is H; 3,5-dichloro-1,2,4-triazine can be prepared according to methods described in Journal of Organic Chemistry, 23, 1522-4; 1958 in which 1,2,4-triazine-3,5(2H, 4H)dione is reacted with POCl_3 . The synthesis of 3,5-dichloro-1,2,4-triazine is illustrated in Scheme 41.

Scheme 41

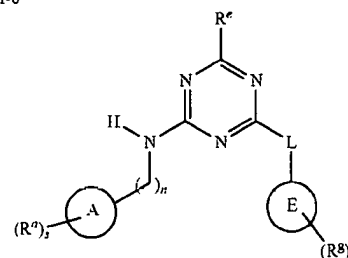


A compound of Formula I, 1A, 1C, 1IC or VIB can be prepared in a 2 steps synthesis as shown in Scheme 42. A [Ring A]-(CH_2) $_n$ NH— moiety can first be incorporated to the central triazine moiety by reacting [Ring A]-(CH_2) $_n$ NH $_2$ with 2,4-dichloro-6-substituted-1,3,5-triazine in the presence of a base as for example di-isopropylethylamine in a suitable solvent. The [Ring E]-L-moiety can then be incorporated onto 1-6 using various conditions depending on the nature of the L linker. The variables in the intermediate [Ring E]-[L]- and [Ring A] are as defined previously, Rings A and E being substituted with permitted R^a and R^8 groups respectively.

Scheme 42



I-6

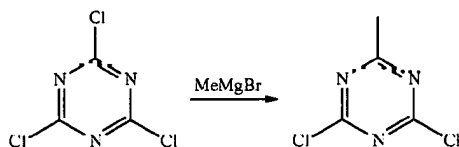


When R^e is methyl, 2,4-dichloro-6-methyl-1,3,5-triazine can be prepared according to methods described in Bioorganic Medicinal Chemistry letters 16(21), 5664-5667, 2006. 2,4,6-trichloro-1,3,5-triazine is reacted with methyl magne-

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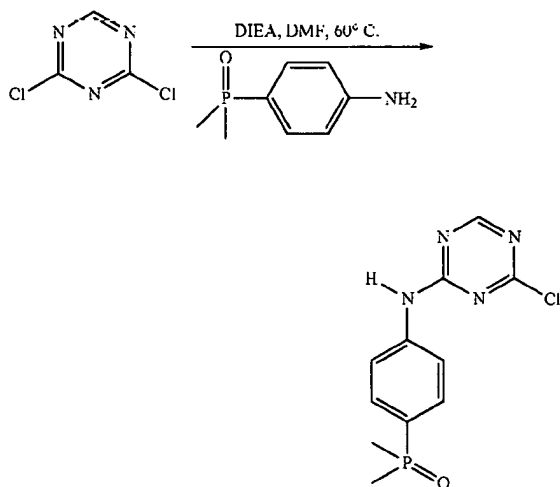
sium bromide to generate 2,4-dichloro-6-methyl-1,3,5-triazine as illustrated in Scheme 42A.

Scheme 42A



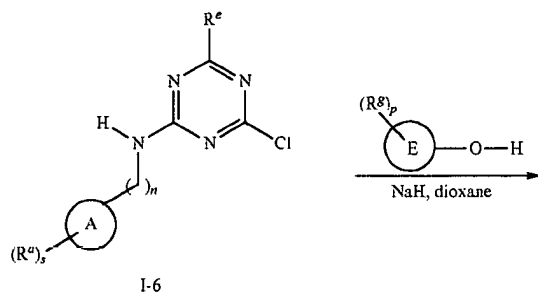
In a non limiting example, an intermediate of formula I-6 in which R^e is H, n is 0 and Ring A is phenyl is illustrated in Scheme 42B:

Scheme 42B



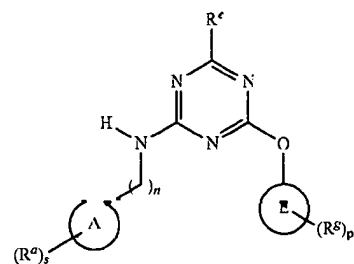
A compound of Formula VIB in which L is O can be prepared using microwave chemistry, by reacting an intermediate I-6 with [Ring E]-OH in a solvent such as dimethylformamide and high temperatures as shown in Scheme 43.

Scheme 43



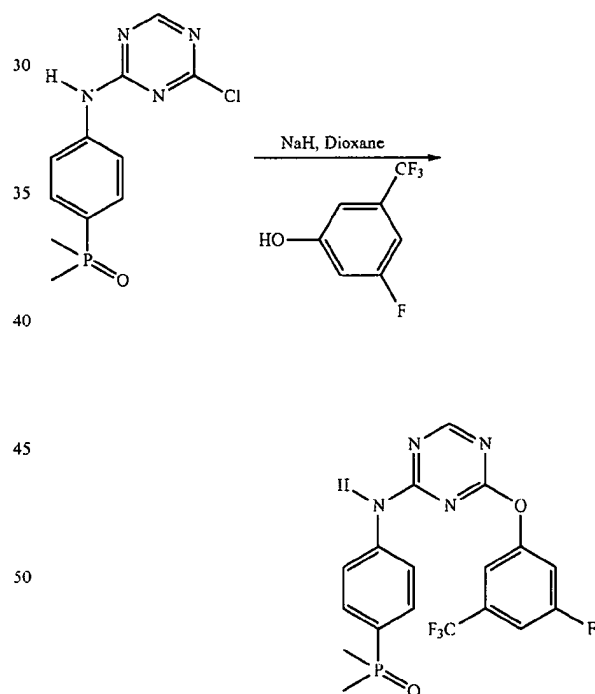
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An approach to the preparation of a compound of Formula VIB in which L is O, is illustrated below in Scheme 43A in which Ring A and Ring E are phenyls:

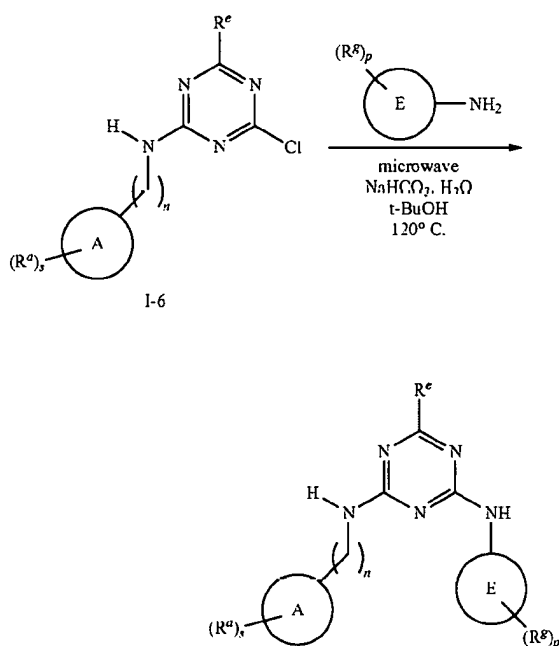
Scheme 43A



A compound of Formula VIB in which L is NH can be prepared using microwave chemistry, by reaction an intermediate I-6 with [Ring E]-NH₂, in a polar solvent such as Ethanol, and using high temperatures, as shown in Scheme 44. A base (i.e. di-isopropylethyl amine, triethylamine, or the like) or an acid may be added to facilitate the displacement reaction. A similar displacement reaction is described in PCT patent application WO 2005/047279.

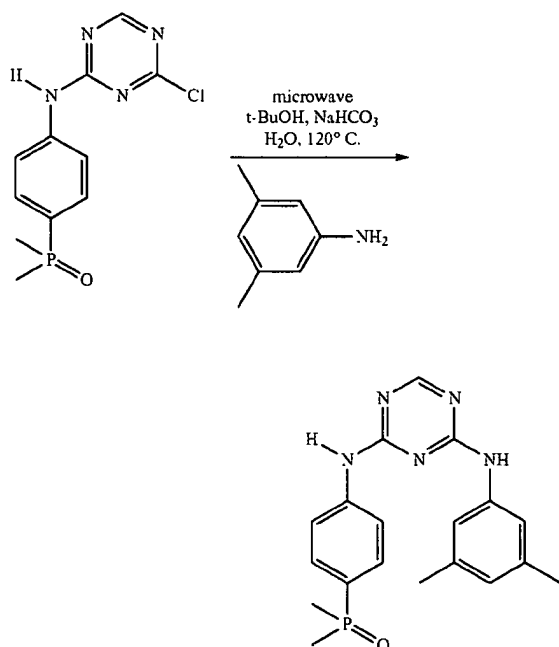
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Scheme 44



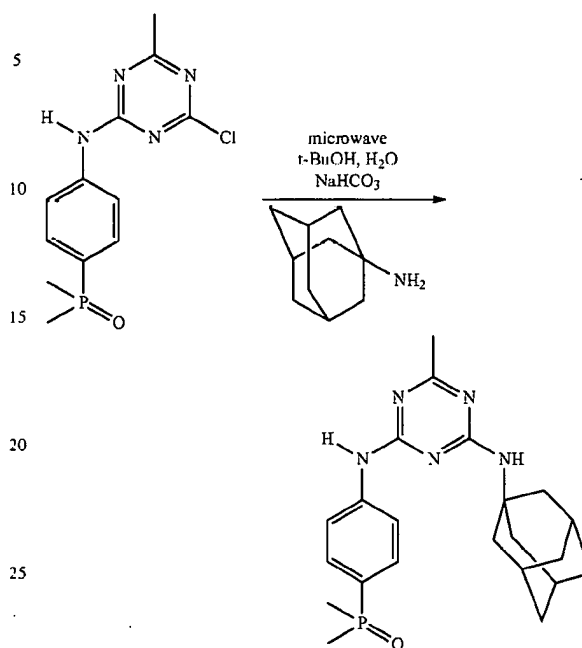
An approach to the preparation of a few compounds of Formula VIB in which L is NH, is illustrated below in Scheme 44A and 44B in which Ring E is a phenyl or adamantane respectively:

Scheme 44A



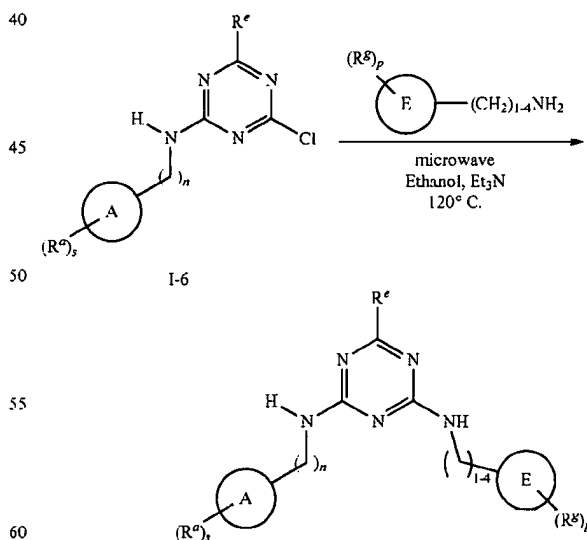
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Scheme 44B



A compound of Formula VIB in which L is NH(CH₂)₁₋₄ can be prepared using microwave chemistry, by reaction an intermediate I-6 with [Ring E]-(CH₂)₁₋₄NH₂, in the presence of a base such as triethylamine, in a polar solvent such as Ethanol, and using high temperatures, as shown in Scheme 45:

Scheme 45

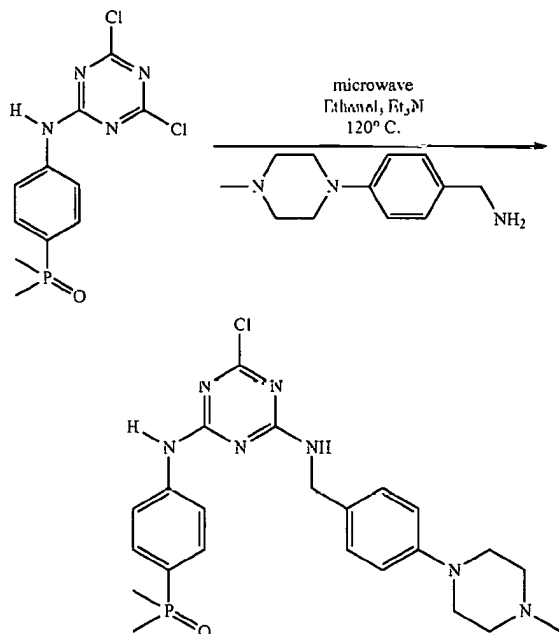


An approach to the preparation of a few compounds of Formula VIB in which L is NH(CH₂)₁₋₄, is illustrated below in Schemes 45A and 45B. Scheme 45A illustrates the synthesis of a compound of Formula VIB in which R^e is Cl, Ring E is a phenyl and L is NHCH₂ and Scheme 45B illustrates the

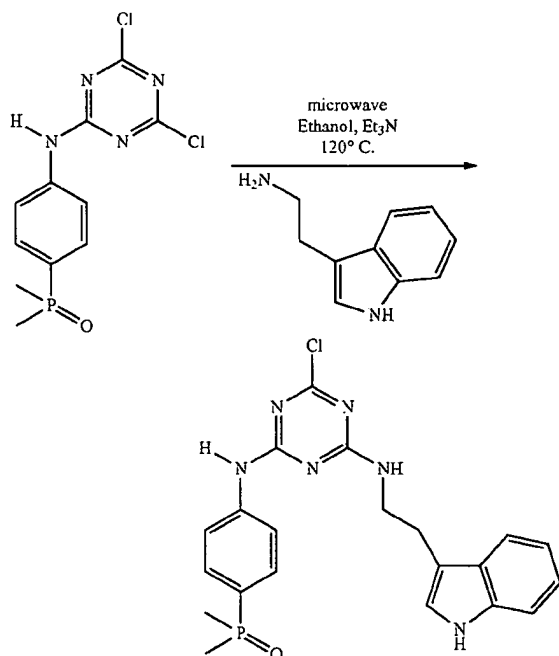
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synthesis of a compound of Formula VIB in which R^e is Cl, Ring E is 3-1H-indole and L is $\text{NH}(\text{CH}_2)_2$:

Scheme 45A



Scheme 45B

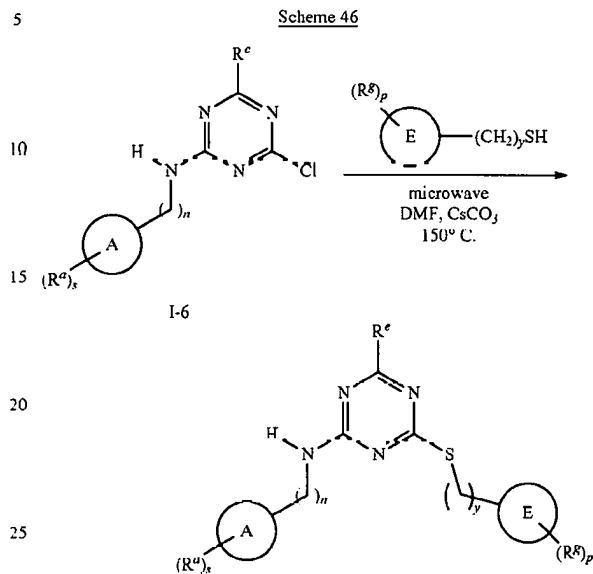


A compound of Formula VIB in which L is $\text{SH}(\text{CH}_2)_y$, can be prepared using microwave chemistry, by reaction an intermediate I-6 with [Ring E]-(CH_2)_ySH, in the presence of a base such as Cesium carbonate, and in a solvent such as

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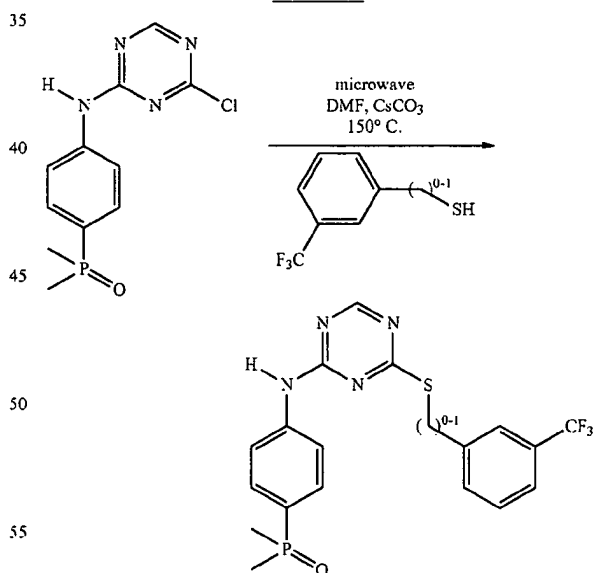
dimethylformamide at high temperatures, as shown in Scheme 46. The variable y is defined above.

Scheme 46



An approach to the preparation of a compound of Formula VIB in which L is $\text{S}(\text{CH}_2)_y$, is illustrated below in Scheme 46A:

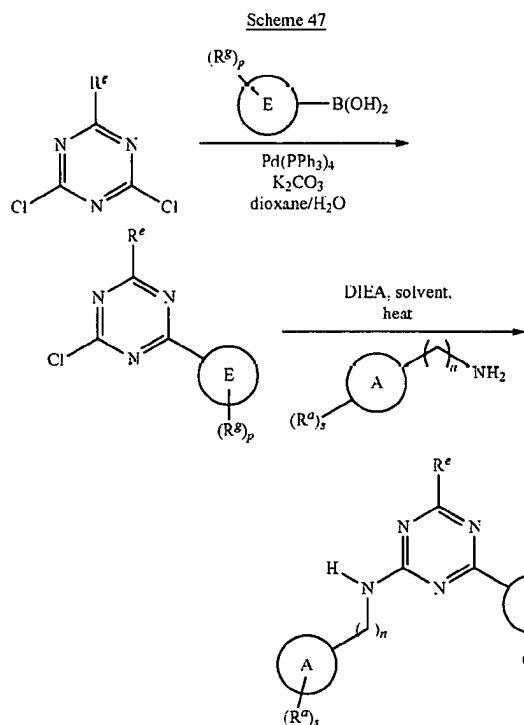
Scheme 46A



A compound of Formula VIB in which L is bond and [Ring E] is an aryl or heteroaryl, can be prepared using Suzuki coupling conditions. Scheme 11 illustrates the Suzuki coupling reaction. The displacement of one of the chlorine by an aryl Grignard or an aryl boronic acid is described in PCT patent application WO 01/25220 and Helv. Chim. Acta, 33, 1365 (1950). The displacement of one of the chlorines by a heteroaryl ring is described in WO 01/25220, J. Het. Chem., 11, 417 (1974); and Tetrahedron 31, 1879 (1975). These

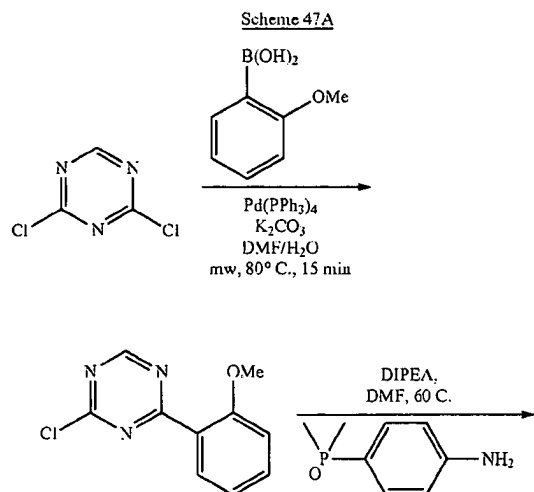
139

reactions can be facilitated by using Microwave chemistry. Microwave assisted Suzuki coupling reaction is also described in Journal of Medicinal Chemistry, 2007, 50(17), 3497.



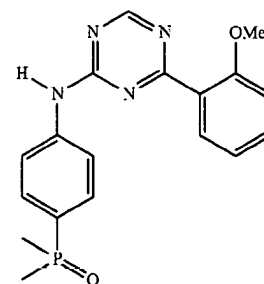
When R^e is chloro, the Suzuki reaction is also described in PCT patent application WO 2002/22605.

In a non limiting example, Scheme 47A illustrates the preparation of a compound of Formula VIB in which L is a bond and [Ring E] is a substituted phenyl.

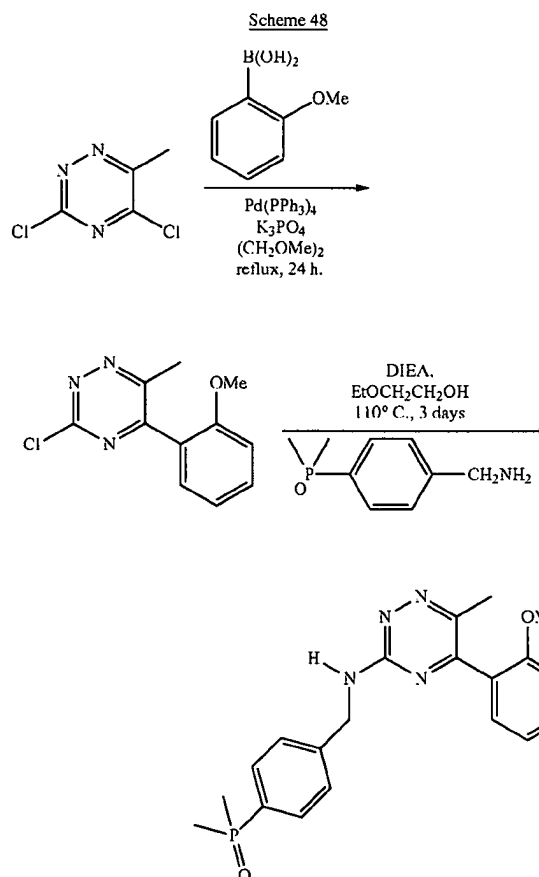


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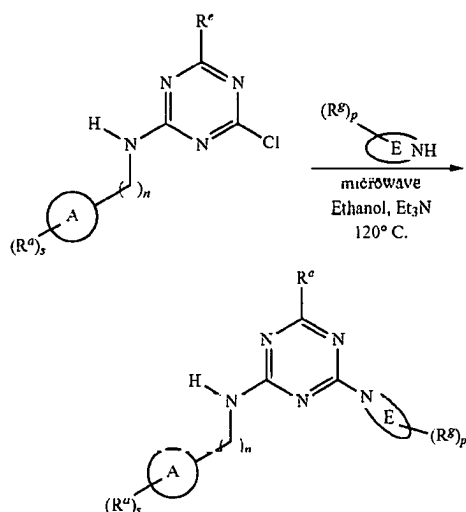
A compound of Formula I, IB or VIA in which L is a bond and Ring E is an aryl or heteroaryl ring, can also be prepared in a similar way using Suzuki coupling conditions. A similar sequence of reaction is described in PCT patent application WO 2005/054199 and is illustrated below in Scheme 48:



A compound of Formula VIA in which L is bond and [Ring E] is a N-linked heterocyclyl, can be prepared using microwave chemistry, by reaction an intermediate I-6 with the heterocyclyl, in the presence of a base such as triethylamine, in a polar solvent such as Etanol, and using high temperatures, as shown in Scheme 49. A similar displacement is described in PCT patent application WO 2005/059668.

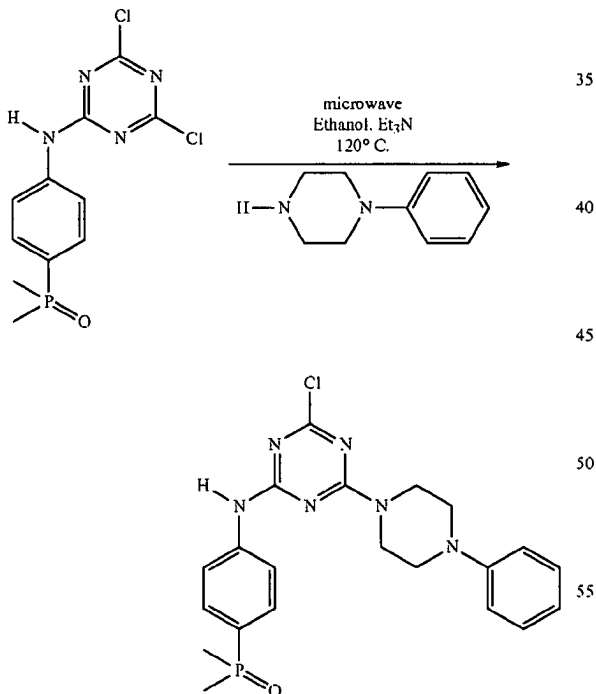
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Scheme 49



In a non limiting example, Scheme 49A illustrates the preparation of a compound of Formula VIA in which L is a bond, R^e is Cl and [Ring E] is N-phenyl-piperazine.

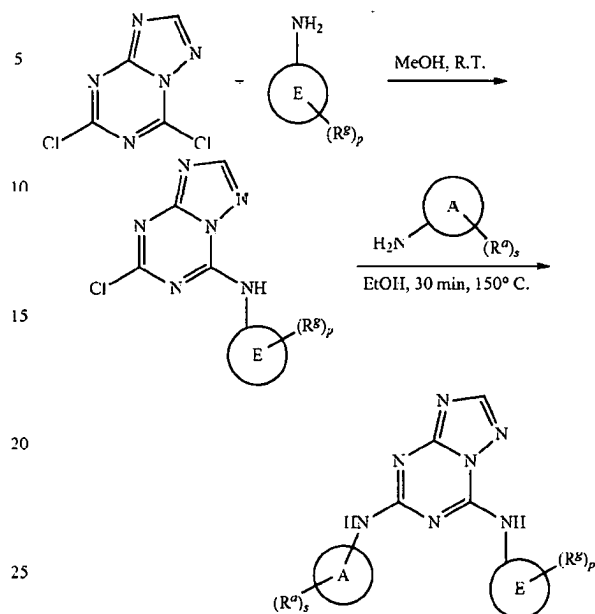
Scheme 49A



Scheme 50 illustrates the preparation of a compound of Formula IVA in which R^e is L-[Ring E]; L is NH, X³ is N, X⁴ is C and Ring C is a triazole. A similar sequence of reaction is described in Bioorganic & Medicinal Chemistry Letters, 16(5), 1353-1357; 2006. Microwave chemistry can also be used to accelerate the displacement reaction.

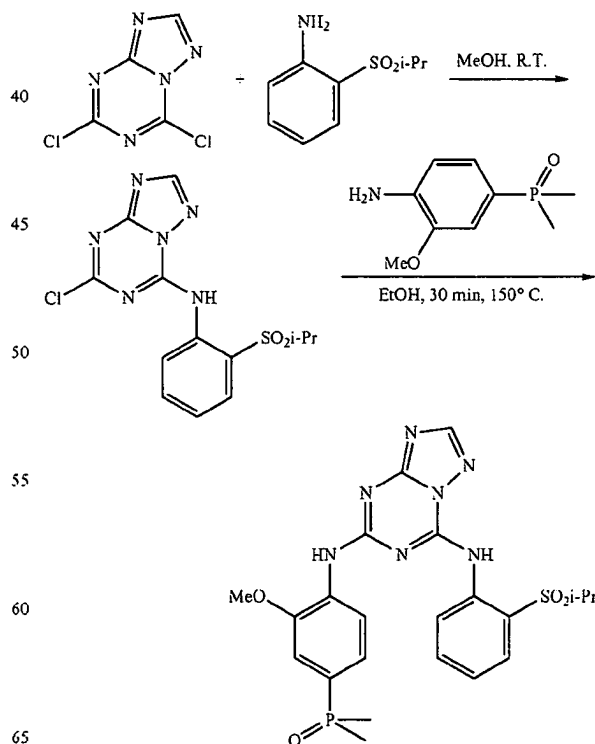
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Scheme 50



In a non limiting example, Scheme 50A illustrates the preparation of compounds of Formula IVA in which L is NH, X³ is N, X⁴ is C, Ring C is a triazole, and Ring A and Ring E are substituted phenyl.

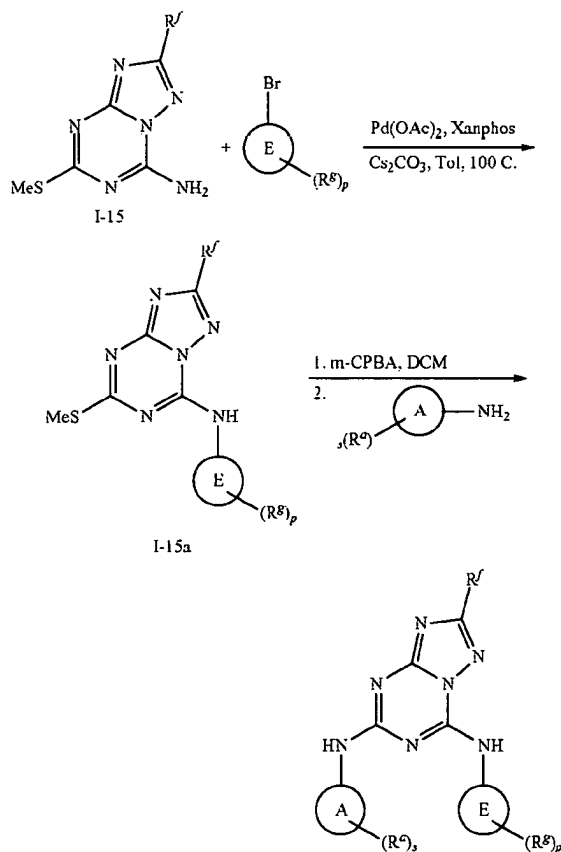
Scheme 50A



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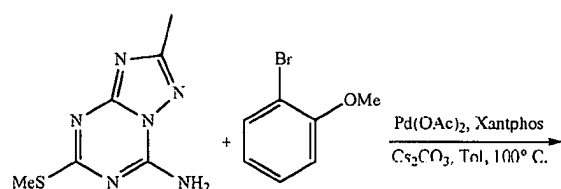
An alternative route to compounds of Formula IVA in which Ring C is a triazole is illustrated in Scheme 51. A compound of Formula I-15 can be reacted with an aryl halide (such as aryl bromide) or heteroaryl halide in the presence of a base, such as for example Cesium carbonate, and in the presence of a palladium acetate and a phosphorous ligand (i.e. xanphos); which generates intermediate I-15a. Intermediate I-15a is then subjected to m-CPBA and the oxidized sulfur is displaced with a Ring A-NH₂ moiety. The synthesis of intermediate I-15 is described in *Journal of heterocyclic chemistry*, 37(6), 1587-1590, 2000.

Scheme 51



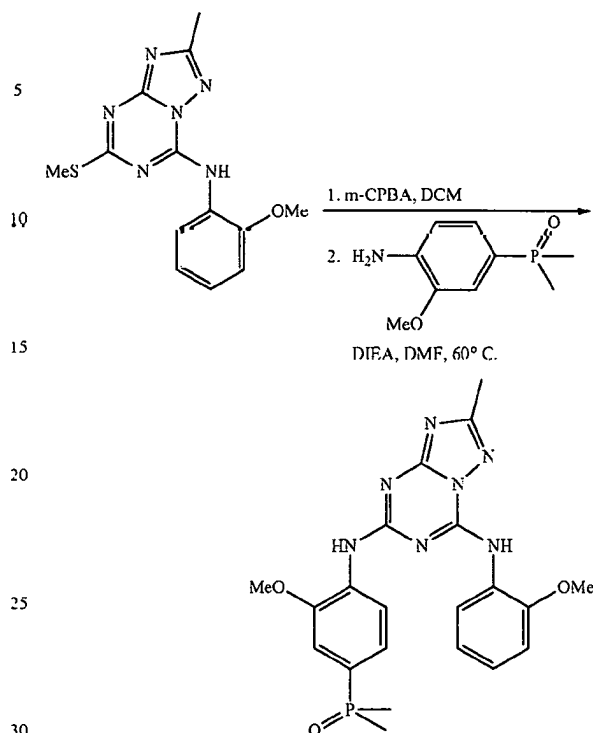
In a non limiting example, Scheme 51A illustrates the preparation of compounds of Formula IVA in which R^c is L-[Ring E], and L is NH, X³ is N, X⁴ is C, Ring C is a triazole, R^f is Me and Ring A and Ring E are substituted phenyl.

Scheme 51A



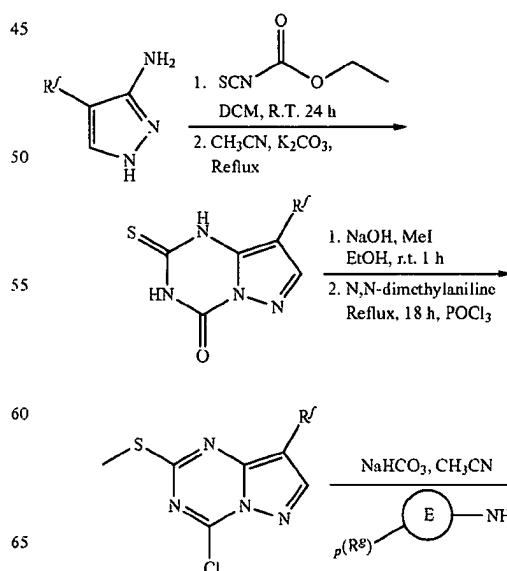
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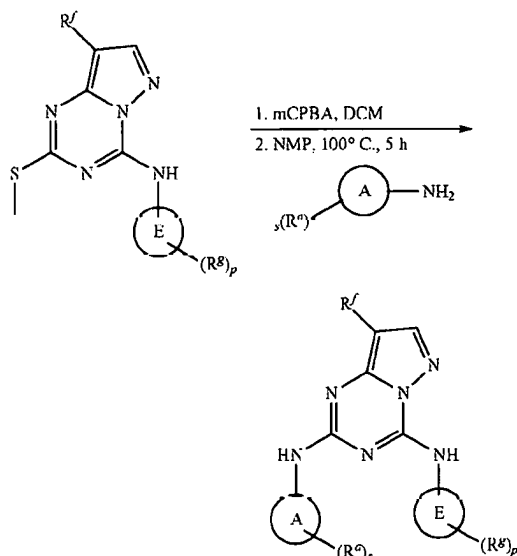
Scheme 52 illustrates the synthesis of a compound of Formula IVA in which X³ is N, X⁴ is C and Ring C is a pyrazole. The pyrazolo[1,5-a][1,3,5]triazine ring system can be prepared from the starting amino pyrazole as shown in Scheme 52. Synthesis of various amino pyrazoles and cyclization conditions are described in US patent application 2008/187219 and *Biorganic & Medicinal Chemistry letters*, 17(15), 4191-4195, 2007.

Scheme 52



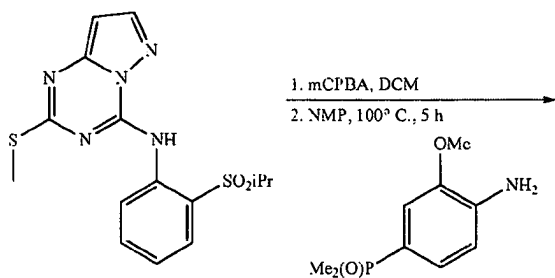
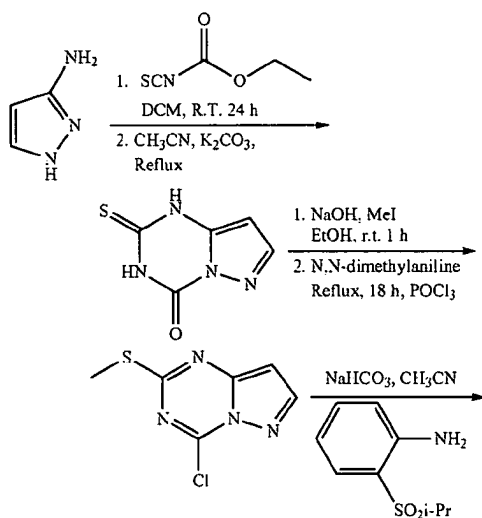
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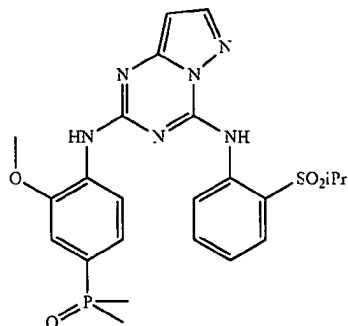
In a non limiting example, Scheme 52A illustrates the preparation of compounds of Formula IVA in which X³ is N, X⁴ is C, Ring C is a pyrazole, Ring A and Ring E are substituted phenyl.

Scheme 52A



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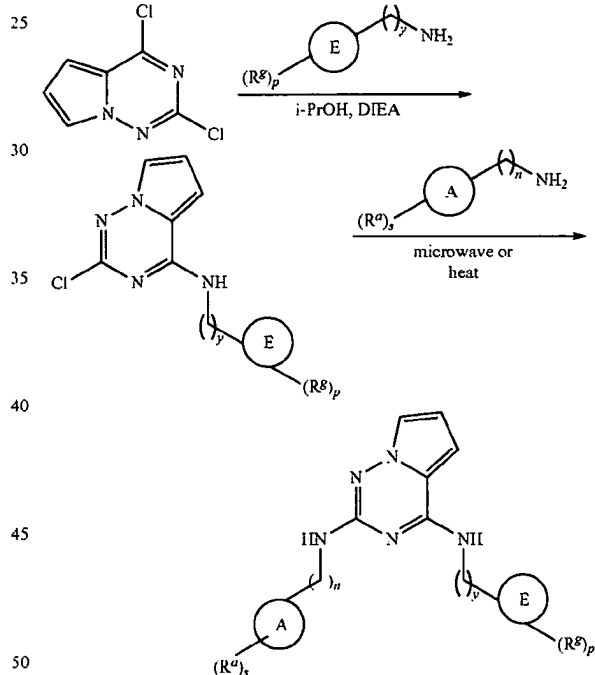
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Scheme 53 illustrates the synthesis of a compound of Formula IVA in which X⁴ is N and X³ is C, R^c is L-[Ring E], L is NH and [Ring C] is a pyrrole. This synthesis is described in PCT application WO 2008/057994.

Scheme 53



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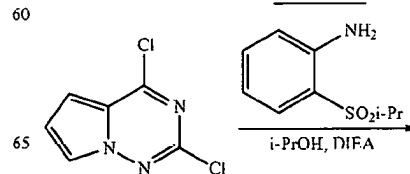
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In a non limiting example, Scheme 53A illustrates the preparation of compounds of Formula IVA in which X⁴ is N and X³ is C, R^c is L-[Ring E], L is NH and [Ring C] is a pyrrole; and Ring A and Ring E are substituted phenyl.

Scheme 53A

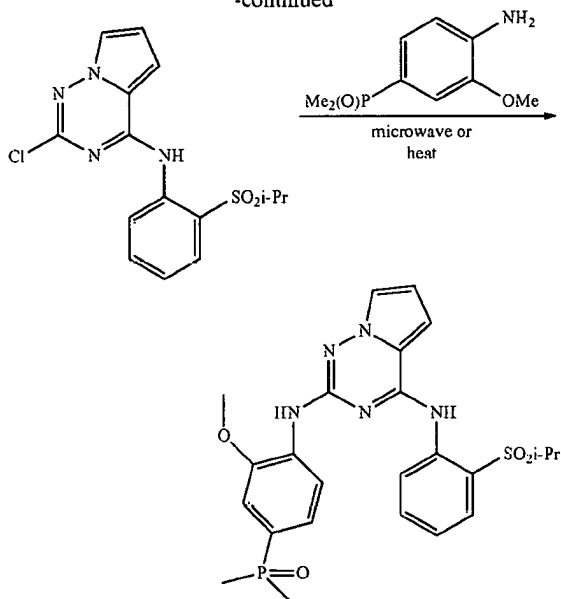


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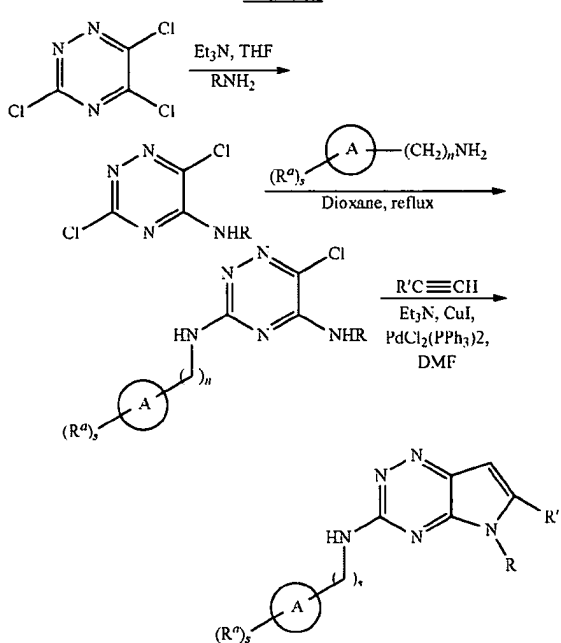
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Scheme 54 illustrates the synthesis of a compound of Formula IIIA in which Ring B is a pyrrole. 3,6-Dichloro-N-substituted-1,2,4-triazine-5-amine is reacted with a substituted alkyne under Sonogashira conditions to generate 3-chloro-5-substituted-pyrrolo[2,3-e][1,2,4]triazine. A similar synthetic route using Sonogashira reaction is described in Tetrahedron Letters, 48(29), 5069-5072; 2007.

Scheme 54



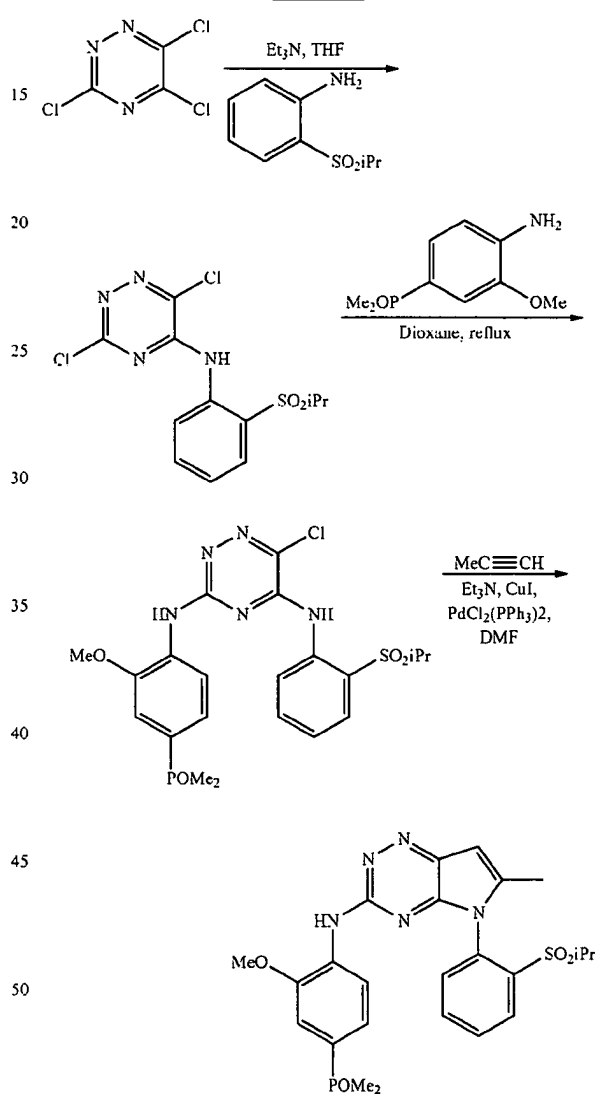
in which Ring A and R^a , n and s are as defined in part I and R and R' are alkyl, heteroaryl, aryl, aryl alkyl, heteroaryl alkyl, heterocyclyl and other groups selected from the R' list of substituents. Examples of R' are methyl, ethyl, methyl dialky-

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lamino, phenyl and the like. Examples of R are substituted phenyl, substituted benzyl, substituted pyridine and the like.

In a non limiting example, Scheme 54A illustrates the preparation of compounds of Formula IIIA in which Ring B is a pyrrole; R' is a methyl group, R is a substituted phenyl and Ring A is a substituted phenyl.

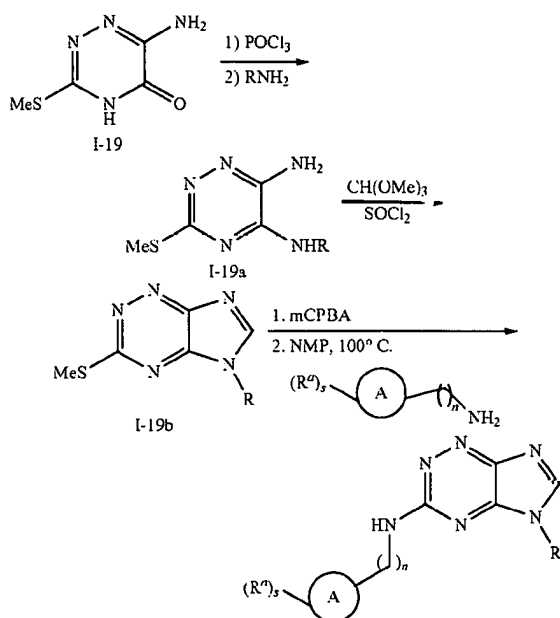
Scheme 54A



Another example of preparation of a compound of Formula IIIA is illustrated below in Scheme 55 in which Ring B is an imidazole. An intermediate I-19 can be reacted with an amine to generate intermediate I-19a and the cyclization occurs in the presence of SOCl_2 and trimethoxymethane and generates intermediate I-19b. The cyclization step is described in Liebigs Annalen der Chemie, 7, 631-40, 1990. The methyl thioether in intermediate I-19b can then be oxidized with m-CPBA and displaced with a $[\text{Ring A}]-(\text{CH}_2)_n\text{NH}_2$ moiety as previously described in Scheme 52.

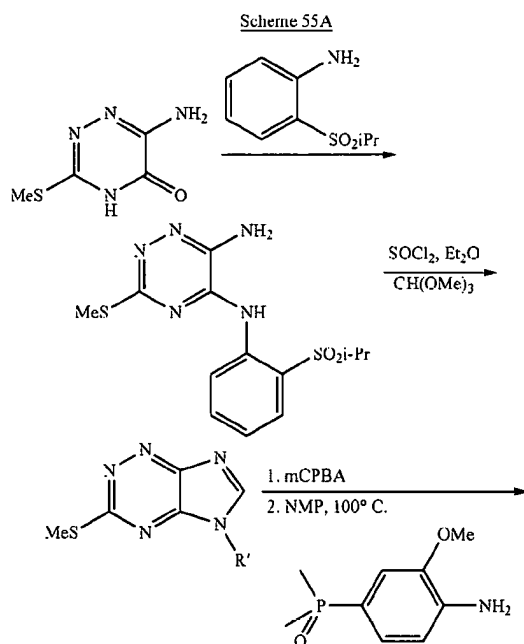
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Scheme 55



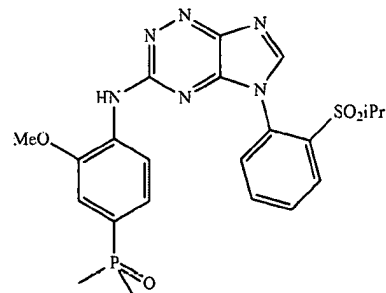
in which R is alkyl, heteroaryl, aryl, aryl alkyl, heteroaryl alkyl, heterocyclyl and other groups selected from the R' list of substituents. Examples of R are methyl, ethyl, methyl dialkylamino, phenyl and the like. Examples of R are substituted phenyl, substituted benzyl, substituted pyridine and the like. Ring A and R^a are defined in part 1.

In a non limiting example, Scheme 55A illustrates the preparation of compounds of Formula IIIA in which Ring B is an imidazole, Ring A is a substituted phenyl and R is a substituted phenyl:



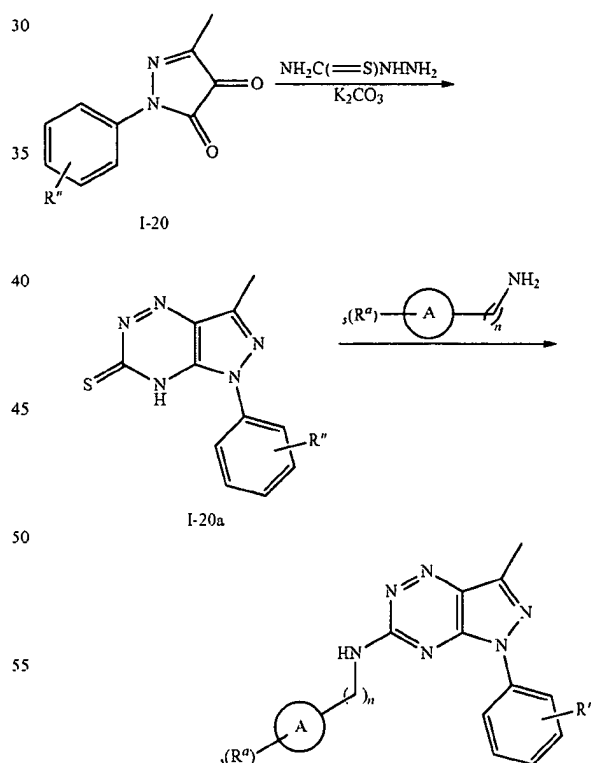
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Another example of preparation of a compound of Formula IIIA is illustrated below in Scheme 56 in which Ring B is a pyrazole. An intermediate I-20 can be reacted with hydrazinecarbothioamide and the cyclization occurs in the presence of potassium carbonate which generates intermediate I-20a. The cyclization step is described in Journal of Heterocyclic Chemistry, 21(3), 923-6, 1984. Intermediate I-20a is then reacted with a [Ring]A-(CH₂)_nNH₂ moiety. A similar displacement is described in Journal fuer Praktische Chemie (Leipzig), 326(6), 994-8, 1984.

Scheme 56

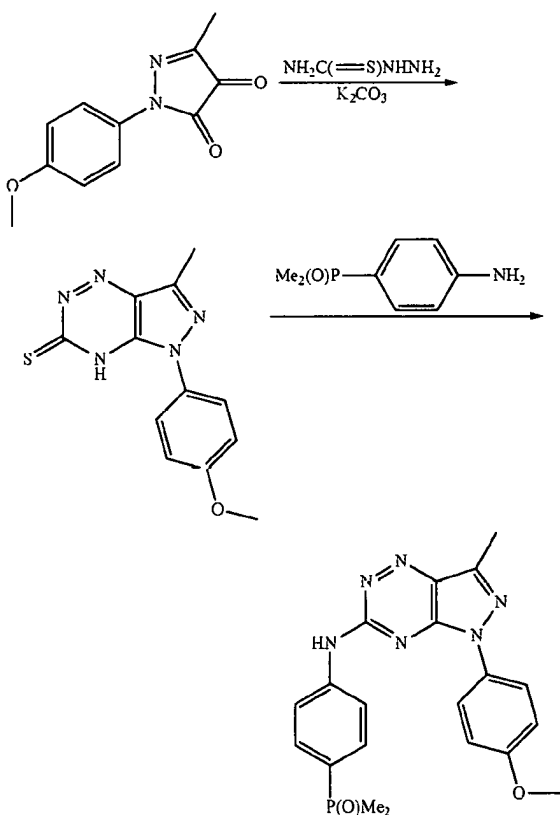


in which R'' is a substituent selected from R' list and Ring A and R^a are defined in part 1.

In a non limiting example, Scheme 56A illustrates the preparation of compounds of Formula IIIA in which Ring B is a pyrazole, Ring A is a substituted phenyl and R'' is a methoxy group.

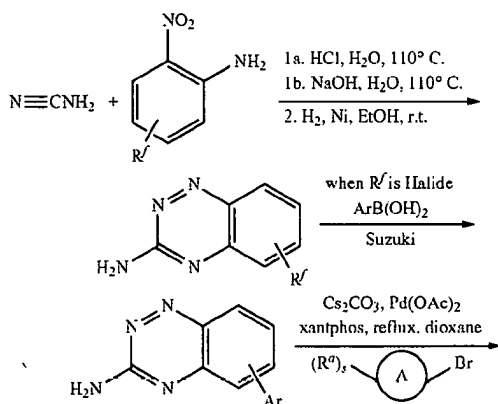
151

Scheme 56A



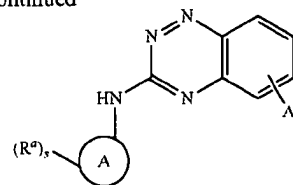
Another example of preparation of a compound of Formula IIIA is illustrated below in Scheme 57 in which Ring B is a phenyl. A substituted 2-nitroaniline can undergo cyclization in the presence of Raney Nickel as described in Bioorganic & Medicinal Chemistry Letters, 17(21), 5818, 2007. When 2-nitroaniline is substituted with a bromide or halide, a Suzuki coupling reaction can be used to introduce an aryl or heteroaryl onto the fused phenyl ring B. The Ring A-NH₂ moiety can be introduced using Buchwald-Hartwig cross-coupling reaction.

Scheme 57



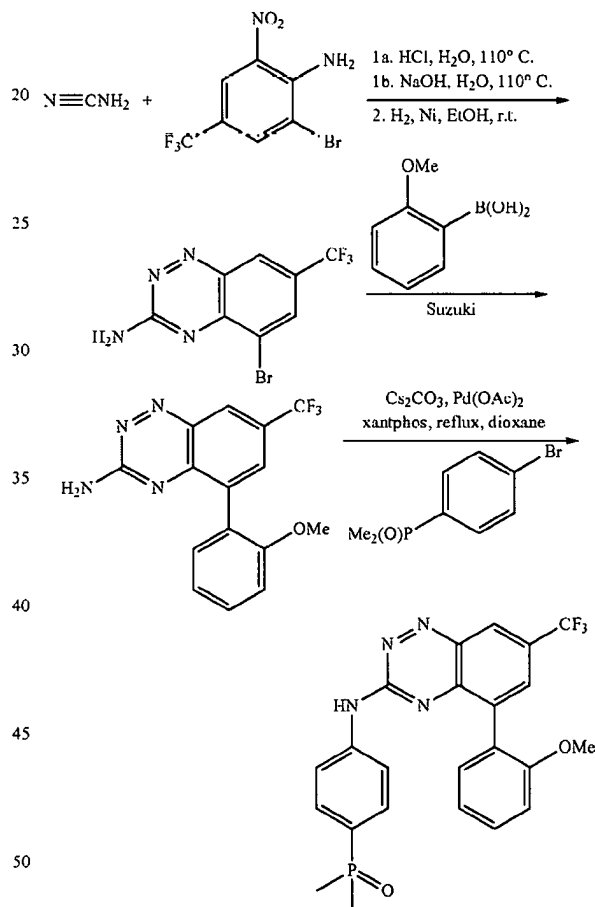
152

-continued



In a non limiting example, Scheme 57A illustrates the preparation of compounds of Formula IIIA in which Ring B and Ring A are substituted phenyl:

Scheme 57A



With synthetic approaches such as the foregoing, combined with the examples which follow, additional information provided herein and conventional methods and materials, the practitioner should be able to prepare the full range of compounds disclosed herein.

5. Uses, Formulations, Administration

Pharmaceutical Uses; Indications

The invention features compounds having biological properties which make them of interest for treating or modulating disease in which kinases may be involved, symptoms of such disease, or the effect of other physiological events mediated by kinases. For instance, a number of compounds of the

invention have been shown to inhibit tyrosine kinase activity of ALK, fak and c-met, among other tyrosine kinases which are believed to mediate the growth, development and/or metastasis of cancer. A number of compounds of the invention have also been found to possess potent in vitro activity against cancer cell lines, including among others karpas 299 cells. Such compounds are thus of interest for the treatment of cancers, including solid tumors as well as lymphomas and including cancers which are resistant to other therapies.

Such cancers include, among others, cancers of the breast, non small cell lung cancer (NSCLS), neural tumors such as glioblastomas and neuroblastomas; esophageal carcinomas, soft tissue cancers such as rhabdomyosarcomas, among others; various forms of lymphoma such as a non-Hodgkin's lymphoma (NHL) known as anaplastic large-cell lymphoma (ALCL), various forms of leukemia; and including cancers which are ALK or c-met mediated.

Anaplastic Lymphoma Kinase (ALK) is a cell membrane-spanning receptor tyrosine kinase, which belong to the insulin receptor subfamily. ALK receptor tyrosine kinase (RTK) was initially identified due to its involvement in the human non-Hodgkin lymphoma subtype known as anaplastic large-cell lymphoma (ALCL). ALK normally has a restricted distribution in mammalian cells, being found at significant levels only in nervous system during embryonic development, suggesting a possible role for ALK in brain development (Duyster, J. Et al., *Oncogene*, 2001, 20, 5623-5637).

In addition to its role in normal development, expression of the full-length normal ALK has also been detected in cell lines derived from a variety of tumors such as neuroblastomas, neuroectodermal tumors (Lamant L. Et al., *Am. J. Pathol.*, 2000, 156, 1711-1721; Osajima-Hakomori Y., et al., *Am. J. Pathol.* 2005, 167, 213-222) and glioblastoma (Powers C. et al., *J. Biol. Chem.* 2002, 277, 14153-14158; Grzelinski M. et al., *Int. J. Cancer*, 2005, 117, 942-951; Mentlein, R. Et al., *J. Neurochem.*, 2002, 83, 747-753) as well as breast cancer and melanoma lines (Dirk W. G. Et al., *Int. J. Cancer*, 2002, 100, 49-56).

In common with other RTKs, translocations affect the ALK gene, resulting in expression of oncogenic fusion kinases the most common of which is NPM-ALK. For example, approximately sixty percent of anaplastic large cell lymphomas (ALCL) are associated with a chromosome mutation that generates a fusion protein consisting of nucleophosmin (NMP) and the intracellular domain of ALK. (Armitage, J. O. et al., *Cancer: principle and practice of oncology*, 6th Edition, 2001, 2256-2316; Kutok, J. L. & Aster J. C., *J. Clin. Oncol.*, 2002, 20, 3691-3702; Wan, W. et al., *Blood*, 2006, 107, 1617-1623. This mutant protein, NMP-ALK, possesses a constitutively active tyrosine kinase domain that is responsible for its oncogenic property through activation of downstream effectors (Falini, B and al., *Blood*, 1999, 94, 3509-3515; Morris, S. W. et al., *Brit. J. Haematol.*, 2001, 113, 275-295). Experimental data have demonstrated that the aberrant expression of constitutively active ALK is directly implicated in the pathogenesis of ALCL and that inhibition of ALK can markedly impair the growth of ALK positive lymphoma cells (Kuefer, Mu et al., *Blood*, 1997, 90, 2901-2910; Bai, R. Y. et al., *Exp. Hematol.*, 2001, 29, 1082-1090; Slupianek, A. et al., *Cancer Res.*, 2001, 61, 2194-2199; Turturro, F. et al., *Clin. Cancer Res.*, 2002, 8, 240-245). The constitutively activated chimeric ALK has also been demonstrated in about 60% of inflammatory myofibroblastic tumors (IMTs), a slow growing sarcoma that mainly affects children and young adults (Lawrence, B. et al., *Am. J. Pathol.*, 2000, 157, 377-384). Furthermore, recent reports have also described the occurrence of a variant ALK fusion, TPM4-ALK, in cases of squamous cell carci-

noma (SCC) of the esophagus (Jazzi fr., et al., *World J. Gastroenterol.*, 2006, 12, 7104-7112; Du X., et al., *J. Mol. Med.*, 2007, 85, 863-875; Aklilu M., *Semin. Radiat. Oncol.*, 2007, 17, 62-69). Thus, ALK is one of the few examples of an RTK implicated in oncogenesis in both non-hematopoietic and hematopoietic malignancies. More recently it has been shown that a small inversion within chromosome 2p results in the formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene in non-small-cell lung cancer (NSCLC) cells (Soda M., et al., *Nature*, 2007, 448, 561-567).

We therefore envision that an ALK inhibitor would either permit durable cures when used as a single therapeutic agent or combined with current chemotherapy for ALCL, IMT, proliferative disorders, glioblastoma and other possible solid tumors cited herein, or, as a single therapeutic agent, could be used in a maintenance role to prevent recurrence in patients in need of such a treatment.

Pharmaceutical Methods

The invention features methods for treating a subject having or at risk of contracting cancer by administering to the subject a therapeutically effective amount of a compound of the invention.

A "therapeutically effective amount" is that amount effective for detectable killing or inhibition of the growth or spread of cancer cells; the size or number of tumors; or other measure of the level, stage, progression or severity of the cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular anticancer agent, its mode of administration, combination treatment with other therapies, and the like.

The compound, or a composition containing the compound, may be administered using any amount and any route of administration effective for killing or inhibiting the growth of tumors or other forms of cancer.

The anticancer compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of anticancer agent appropriate for the patient to be treated. As is normally the case, the total daily usage of the compounds and compositions of the invention will be decided by the attending physician using routine reliance upon sound medical judgment. The specific therapeutically effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated; the severity of the disorder; the potency of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the route and schedule of administration; the rate of metabolism and/or excretion of the compound; the duration of the treatment; drugs used in combination or coincident with administration of the compound of the invention; and like factors well known in the medical arts.

Furthermore, after formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, the compositions of the invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by transdermal patch, powders, ointments, or drops), sublingually, buccally, as an oral or nasal spray, or the like.

The effective systemic dose of the compound will typically be in the range of 0.01 to 500 mg of compound per kg of patient body weight, preferably 0.1 to 125 mg/kg, and in some cases 1 to 25 mg/kg, administered in single or multiple doses.

Generally, the compound may be administered to patients in need of such treatment in a daily dose range of about 50 to about 2000 mg per patient. Administration may be once or multiple times daily, weekly (or at some other multiple-day interval) or on an intermittent schedule. For example, the compound may be administered one or more times per day on a weekly basis (e.g. every Monday) indefinitely or for a period of weeks, e.g. 4-10 weeks. Alternatively, it may be administered daily for a period of days (e.g. 2-10 days) followed by a period of days (e.g. 1-30 days) without administration of the compound, with that cycle repeated indefinitely or for a given number of repetitions, e.g. 4-10 cycles. As an example, a compound of the invention may be administered daily for 5 days, then discontinued for 9 days, then administered daily for another 5 day period, then discontinued for 9 days, and so on, repeating the cycle indefinitely, or for a total of 4-10 times.

The amount of compound which will be effective in the treatment or prevention of a particular disorder or condition will depend in part on well known factors affecting drug dosage. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. A rough guide to effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. The precise dosage level should be determined by the attending physician or other health care provider and will depend upon well known factors, including route of administration, and the age, body weight, sex and general health of the individual; the nature, severity and clinical stage of the disease; the use (or not) of concomitant therapies; and the nature and extent of genetic engineering of cells in the patient.

When administered for the treatment or inhibition of a particular disease state or disorder, the effective dosage of the compound of the invention may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. In many cases, satisfactory results may be obtained when the compound is administered in a daily dosage of from about 0.01 mg/kg-500 mg/kg, preferably between 0.1 and 125 mg/kg, and more preferably between 1 and 25 mg/kg. The projected daily dosages are expected to vary with route of administration. Thus, parenteral dosing will often be at levels of roughly 10% to 20% of oral dosing levels.

When the compound of the invention is used as part of a combination regimen, dosages of each of the components of the combination are administered during a desired treatment period. The components of the combination may administered at the same time; either as a unitary dosage form containing both components, or as separate dosage units; the components of the combination can also be administered at different times during a treatment period, or one may be administered as a pretreatment for the other.

Regarding the Compounds

Compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable salt, ester, or prodrug. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts of amines, carboxylic acids, phosphonates and other types of compounds, are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19 (1977), incorporated

herein by reference. The salts can be prepared *in situ* during the isolation and purification of compounds of the invention, or separately by reacting the free base or free acid of a compound of the invention with a suitable base or acid, respectively. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower-alkyl sulfonate and aryl sulfonate.

Additionally, as used herein, the term "pharmaceutically acceptable ester" refers preferably to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates. Obviously, esters can be formed with a hydroxyl or carboxylic acid group of the compound of the invention.

Furthermore, the term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of compounds of the invention. The term "prodrug" refers to compounds that are transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. See, e.g., T. Iiguchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, and Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

Pharmaceutical Compositions

The invention also features pharmaceutical compositions including a compound of the invention, or a prodrug, pharmaceutically acceptable salt or other pharmaceutically acceptable ester thereof, and one or more pharmaceutically acceptable carriers or excipients. The pharmaceutical compositions optionally further comprise one or more additional therapeutic agents. In certain instances a compound of the invention may be administered to a subject undergoing one or more other therapeutic interventions (e.g. Gleevec or other kinase inhibitors, interferon, bone marrow transplant, farnesyl transferase inhibitors, bisphosphonates, thalidomide, cancer vaccines, hormonal therapy, antibodies, radiation, etc).

For example, the compound of the invention can be used as one component of a combination therapy in which one or more additional therapeutic agents (e.g., an anticancer agent), the agents being either formulated together or separately, is administered to the subject.

The pharmaceutical compositions of the invention include a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers and excipient that can be used in the pharmaceutical compositions of the invention include, without limitation, solvents, diluents, or other vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Fifteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Some examples of materials which can serve as pharmaceutically acceptable carriers or excipients include, but are not limited to, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition.

Compounds of the invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Compounds of the invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

For oral administration, the pharmaceutical composition may be in the form of for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Each unit dosage may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more commonly from about 5 to 200 mg. The amount of a compound of the invention to be administered will typically be in the range of 0.01 to 500 mg of compound per kg body weight, preferably between 0.1 and 125 mg/kg body weight and in some cases between 1 and 25 mg/kg body weight. As mentioned previously, the daily dose can be given in one administration or may be divided between 2, 3, 4 or more administrations.

In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of the invention to the affected area two to four times a day. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, or pastes) and drops suit-

able for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w. but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at Least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

Compounds of the invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered—continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of the invention may be constituted from known ingredients in a known manner.

While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients.

The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers.

Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (i.e. Captisol), cosolvent solubilization (i.e. propylene glycol) or micellar solubilization (i.e. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents. Combination Therapy

Compounds of the invention can be administered as part of a treatment regimen in which the compound is the sole active pharmaceutical agent, or used in combination with one or more other therapeutic agents as part of a combination therapy. When administered as one component of a combination therapy, the therapeutic agents being administered can be formulated as separate compositions that are administered at the same time or sequentially at different times (e.g., within 72 hours, 48 hours, or 24 hours of one another), or the therapeutic agents can be formulated together in a single pharmaceutical composition and administered simultaneously.

Thus, the administration of compounds of the invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of cancer, such as radiation therapy or cytostatic agents, cytotoxic

agents, other anti-cancer agents and other drugs to ameliorate symptoms of the cancer or side effects of any of the drugs.

If formulated as a fixed dose, such combination products employ compounds of the invention within the accepted dosage ranges. Compounds of the invention may also be administered sequentially with other anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered prior to, simultaneously with, or after administration of the other anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision, when appropriate, followed by either radiation or chemotherapy, and typically administered intravenously (IV). The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of cancer by combination drug chemotherapy. And there are several major categories of such antineoplastic agents, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the invention includes antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, CibaGeigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co.

EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl) fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, pirarixin, plicamycin, Asahi Chemical PL-AC, Takeda TAC788, thioguanine, tiazofurin, Erbamon TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uracitin.

A second family of antineoplastic agents which may be used in combination with compounds of the invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldophosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D 384, Sumimoto DACHP(My₂), diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamon FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G M, Chinoin GYKI-17230, hepsulfam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactof Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine,

semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, taumomustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN II, Ajinomoto AN3, Nippon Soda anisomycins, anthracycline, azino-mycin A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BNY-25551, Bristol-Myers BNY-26605 IBristol-Myers BNY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calicheomycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko, DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB 41, doxorubicin, doxorubicin-fibrinogen, elsamycin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-A1b, Erbamont FCE21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KI-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SR1 International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyridanycin A, Tobishi RA-1, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwemycin, Sumitomo SM5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpenecin, thiazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of (xcarotene, (X-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphetamine, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1F Ilenkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluoron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, BristoMyers BNY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, WarnerLambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI958, clafenur, clavridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytosytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenerpene, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprahin, elliptinium acetate, Tsumura EPMTc, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704t gallium nitrate, genkwadaphnin,

Chugai GLA-43, Glaxo GR-63178, grifolan NMF5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kurcha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU 1121 Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MG1136, minactivin, mitonafide, mitouidone mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nissin Flour Milling N-021, N-acylated-dehydroalanines, nafazotrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, WarnerLambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM Alternatively, the present compounds may also be used in co-therapies with other antineoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCEr, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetorelix, cladribine, clotrimazole, cytarabine ocfofate, DA 3030 (Dong-A), daclizumab, denileukin difitox, deslorelin, dextrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab efformithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafor combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa. natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-NI, interferon alfa-n3, interferon alfacon1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuporelin, levamisole+fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocil, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguanzone, mitolactol, mitoxantrone, molgramostim,

nafarelin, naloxone+pentazocine, nartogristim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofuran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazartene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama, vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; ubarelrix; AE 941 (Acterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminogluthimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinidel filgrastim SDO1 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-R7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotype 105AD7 MAb (CRC Technology), idiotype CEA MAb (Trilex), LYM iodine 131 MAb (Techniclone), polymorphic epithelial mucin-tytrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin, gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfirimycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN)y SU 6668 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Treatment Kits

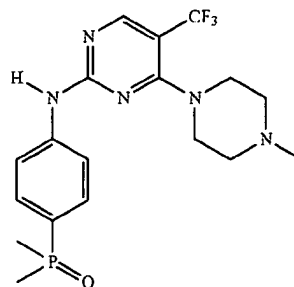
In other embodiments, the invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the invention. In general, the pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention and instructions for administering the pharmaceutical composition (e.g., a label or package insert) as part of a method described herein. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The following representative examples contain important additional information, exemplification and guidance which can be adapted to the practice of the invention in its various embodiments and the equivalents thereof. These examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit its scope. Indeed, various modifications of the invention, and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art upon review of this document, including the examples which follow and the references to the scientific and patent literature cited herein. The contents of those cited references are incorporated herein by reference to help illustrate the state of the art. In addition, for purposes of the invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "Organic Chemistry", Morrison & Boyd (3d Ed), the entire contents of both of which are incorporated herein by reference.

EXAMPLES

Example 1

N-[4-(dimethylphosphoryl)phenyl]-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)pyrimidin-2-amine



4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine

A suspension of 4-amino-dimethylphenylphosphine oxide (3.7 g, 2.2 mmol) in 15 mL of N,N-Dimethylacetamide and 3.6 mL of Diisopropylethylamine, was allowed to stirred at room temperature for 15 minutes until a clear solution was obtained. 2,4-Dichloro-5-(trifluoromethyl)pyrimidine (5.7 g, 2.6 mmol) was added in four portions over 5 minutes. The reaction mixture was stirred at 60 degrees for 1 hour. The reaction mixture was cooled to room temperature and filtered to obtain a white solid. The white solid was washed with 50 mL of water three times and followed by 50 mL of Ethyl ether three times. The white solid was dried under vacuum to yield desired product (3.8 g, 49% yield). MS/ES+: m/z=350.

N-[4-(dimethylphosphoryl)phenyl]-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)pyrimidin-2-amine

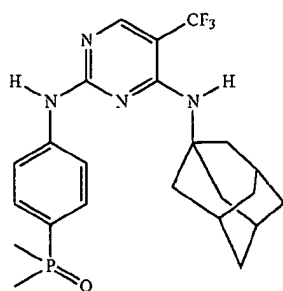
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (25 mg, 0.072

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mmol) in 1.5 mL of ethanol was added 10 μ L of triethylamine and 1-Methyl piperazine (7.2 mg, 0.072 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (24 mg, 79% yield.) MS/ES+: m/z=414.

Example 2

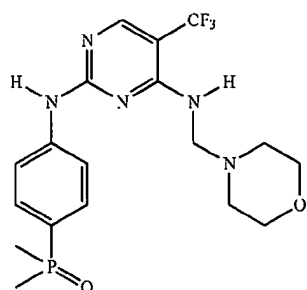
N²-[4-(dimethylphosphoryl)phenyl]-N⁴-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 27 mg, 0.078 mmol) in 1.5 mL of ethanol was added 10 μ L of triethylamine and 1-Adamantanamine (12 mg, 0.078 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (3 mg, 8% yield.) MS/ES+: m/z=465.

Example 4

N²-[4-(dimethylphosphoryl)phenyl]-N⁴-(morpholin-4-ylmethyl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



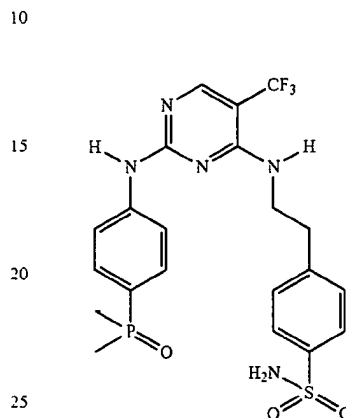
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 4-(2-aminoethyl) morpholine (15 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18

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column with ACN/water mobile phases) to yield a white solid as product (42 mg, 81% yield.) MS/ES+: m/z=430.

Example 5

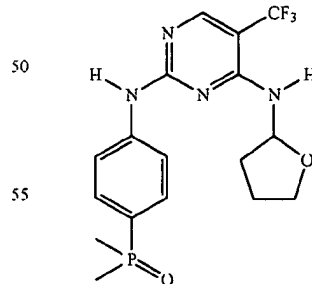
4-(2-{[2-{[4-(dimethylphosphoryl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}ethyl)benzenesulfonamide



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 4-(2-aminoethyl)benzenesulfonamide (23 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (30 mg, 49% yield.) MS/ES+: m/z=514.

Example 6

N²-[4-(dimethylphosphoryl)phenyl]-N⁴-(tetrahydrofuran-2-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



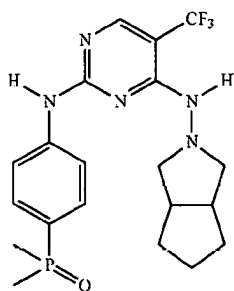
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and (S)-3-aminotetrahydrofuran hydrochloride salt (14 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-

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HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (27 mg, 59% yield.) MS/ES+: $m/z=401$.

Example 7

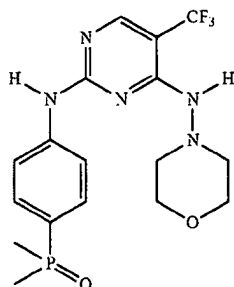
N^2 -[4-(dimethylphosphoryl)phenyl]- N^4 -(hexahydro-cyclopenta[c]pyrrol-2(1H)-yl)-5-(trifluoromethyl)pyrimidin-2,4-diamino



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 3-Amino-3-azabicyclo-[3,3,0]octane hydrochloride salt (19 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (34 mg, 67% yield.) MS/ES+: $m/z=440$.

Example 8

N^2 -[4-(dimethylphosphoryl)phenyl]- N^4 -(morpholin-4-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



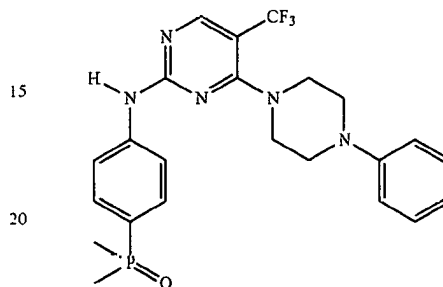
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 4-Aminomorpholine (12 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column

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with ACN/water mobile phases) to yield a white solid as product (6 mg, 12% yield.) MS/ES+: $m/z=416$.

Example 9

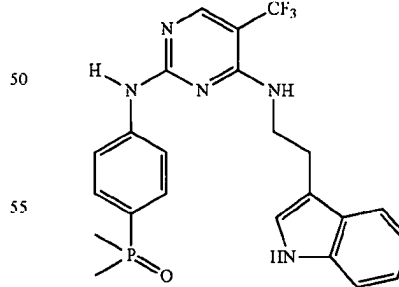
N -[4-(dimethylphosphoryl)phenyl]-4-(4-phenylpiperazin-1-yl)-5-(trifluoromethyl)pyrimidin-2-amine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 1-Phenylpiperazine (19 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (40 mg, 73% yield.) MS/ES+: $m/z=476$.

Example 10

N^2 -[4-(dimethylphosphoryl)phenyl]- N^4 -[2-(1H-indol-3-yl)ethyl]-5-(trifluoromethyl)pyrimidin-2,4-diamine



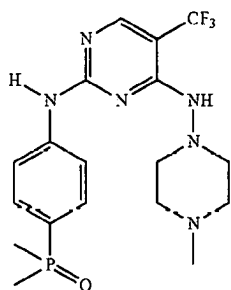
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and Tryptamine (18 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with

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ACN/water mobile phases) to yield a white solid as product (44 mg, 81% yield.) MS/ES+: $m/z=474$.

Example 11

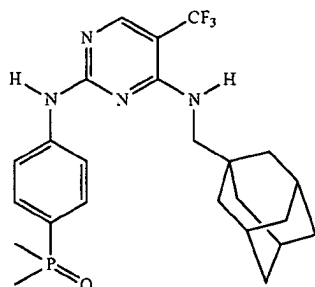
N^2 -[4-(dimethylphosphoryl)phenyl]- N^4 -(4-methylpiperazin-1-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 1-Amino-4-methyl-piperazine (13 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (17 mg, 34% yield.) MS/ES+: $m/z=429$.

Example 12

N^2 -[4-(dimethylphosphoryl)phenyl]- N^4 -(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



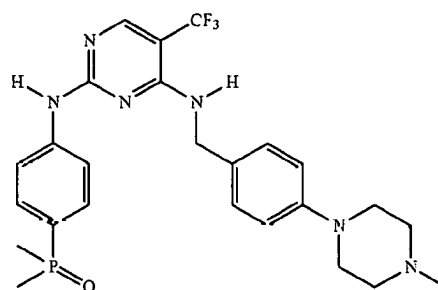
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 1-Adamantanemethylamine (19 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18

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column with ACN/water mobile phases) to yield a white solid as product (40 mg, 73% yield.) MS/ES+: $m/z=479$

Example 13

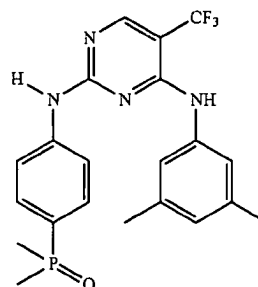
N^2 -[4-(dimethylphosphoryl)phenyl]- N^4 -[4-(4-methylpiperazin-1-yl)benzyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 50 μ L of triethylamine and 4-(4-methylpiperazine)-benzylamine (24 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (21 mg, 73% yield.) MS/ES+: $m/z=519$

Example 14

N^4 -(3,5-dimethylphenyl)- N^2 -[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine



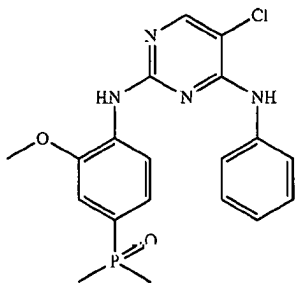
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-5-(trifluoromethyl)pyrimidin-2-amine (prepared as in Example 1: 40 mg, 0.12 mmol) in 2 mL of ethanol was added 10 μ L of Hydrochloric acid in Methanol (2M) and 3,5-Dimethyl aniline (14 mg, 0.12 mmol). The mixture was microwave at 120 degrees for 20 minutes. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC

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(Waters Sunfire C18 column with ACN/water mobile phases) to yield a white solid as product (32 mg, 65% yield.) MS/ES+: $m/z=435$

Example 15

5-chloro-N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-phenylpyrimidine-2,4-diamine



2,5-dichloro-N-phenylpyrimidin-4-amine

To a solution of Aniline (205 mg, 2.2 mmol) and 2,4,5-Trichloropyrimidine (500 mg, 2.7 mmol) in 5 mL of Ethanol, was added 500 mg of Potassium carbonate. The reaction mixture was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography with 10% Ethyl Acetate in Heptane to yield the desired product as an oil (370 mg, 70% yield).

(3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide

To a solution of 5-Chloro-2-nitroanisole (0.5 g, 2.67 mmol) in 5 mL of DMF was added dimethylphosphine oxide (0.229 g, 2.93 mmol), palladium acetate (30 mg, 0.13 mmol), XANTHOS (0.092 g, 0.16 mmol) and potassium phosphate (0.623 g, 2.93 mmol). The mixture was purged with argon, and heated at 120° C. for 18 h. The reaction mixture was basified with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was concentrated and purified by prep-HPLC to give the final product (0.16 g, 30% yield). MS/ES+: $m/z=229$.

4-(dimethylphosphoryl)-2-methoxyaniline

To a solution of (3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide (0.1 g, 0.44 mmol) in 5 mL of EtOH was added 10% weight of palladium on carbon (0.2 g). The mixture was purged with argon, and hydrogenated under 30 psi for 2 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.088 g, 86% yield). MS/ES+: $m/z=199$.

5-chloro-N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-phenylpyrimidine-2,4-diamine

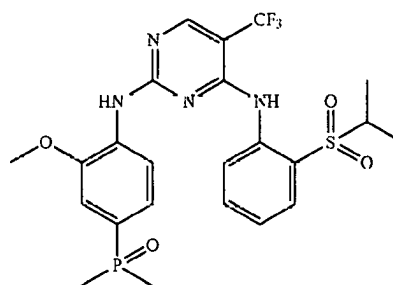
To a solution of 2,5-dichloro-N-phenylpyrimidin-4-amine (84 mg, 0.35 mmol) and 4-(dimethylphosphoryl)-2-methoxy-

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oxyaniline (60 mg, 0.30 mmol) in 1 mL of DMF, was added 0.36 mL of 2.5M HCl in Ethanol. The reaction mixture was heated in a sealed tube at 140 degrees over night. The reaction mixture was filtered through a syringe filter and purified by Prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield the desired product as a white solid. (23 mg, 16% yield). MS/ES+: $m/z=403$

Example 16

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine



2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidin-4-amine

To a solution of 1-Amino-2-(isopropylsulphonyl)benzene (350 mg, 1.6 mmol) in 4 mL of N,N-Dimethyl formamide at 0 degree, was added Sodium hydride (100 mg) and the reaction mixture was allowed to stir at 0 degree for 20 minutes. 2,4-Dichloro-5-(trifluoromethyl)pyrimidine (350 mg, 1.6 mmol) was added in one portion and the reaction mixture was warmed to room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with Ethyl acetate. The combined Ethyl acetate layers were dried over Sodium Sulfate and solvent was removed under reduced pressure. The residue was purified by Prep-HPLC to yield the desired product as a white solid (10 mg, 2% yield).

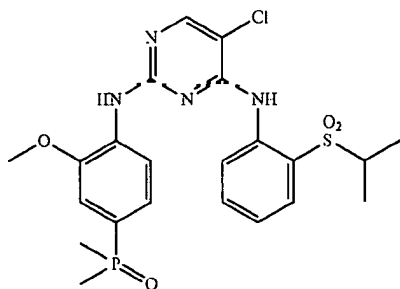
N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine

To a solution of 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidin-4-amine (7.5 mg, 0.02 mmol) and 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 15: 15 mg, 0.7 mmol) in 1 mL of 2-Methoxy ethanol, was added 1 mL of 2.5M HCl in Ethanol. The reaction mixture was heated in a sealed tube at 140 degree over night. The reaction mixture was filtered through a syringe filter and purified by Prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to yield the desired product as a white solid. (0.9 mg, 8% yield). MS/ES+: $m/z=543$

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Example 17

5-chloro-N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine

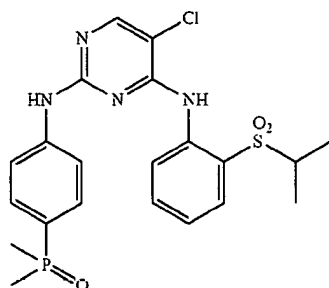
To a solution of 1-Amino-2-(isopropylsulphonyl)benzene (0.955 g, 4.80 mmol) in 2 mL of DMF at 0° C. was added NaH (60% in oil, 0.349 g, 8.72 mmol) in one portion. After stirring for 20 min, 2,4,5-trichloropyrimidine was added. The mixture was stirred at 0° C. for 30 minutes, and then at room temperature for 2 h. After quenching with saturated ammonium chloride solution, the mixture was poured in water and ethyl acetate mixture. Yellow suspension was filtered as final product (0.3 g, 20% yield). MS/ES+: m/z=346.

5-chloro-N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (0.050 g, 0.14 mmol) in 1 mL of 2-methoxyethanol was added 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 15: 0.029 g, 0.14 mmol) and 0.12 mL of 2.5M HCl in EtOH. The mixture was heated in a sealed tube at 140° C. for 1 h. The mixture was basified with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was purified by prep-HPLC to give the final product (20 mg, 24% yield). MS/ES+: m/z=508.

Example 18

5-chloro-N²-[4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

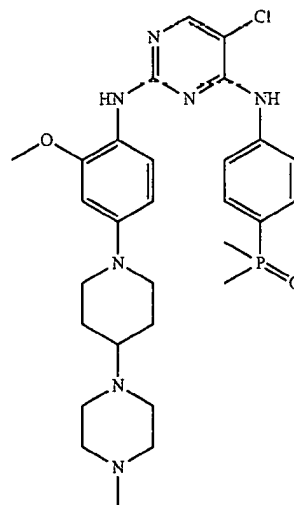


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To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (prepared as in Example 17: 50 mg, 0.14 mmol) in 1 mL of 2-methoxyethanol was added 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 15: 0.025 g, 0.14 mmol) and 0.12 mL of 2.5M HCl in EtOH. The mixture was heated in a sealed tube at 140° C. for 1 h. The mixture was basified with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was purified by prep-HPLC to give the final product (0.100 g, 15% yield). MS/ES+: m/z=478.

Example 19

5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidine-2,4-diamine



2,5-dichloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine

To a solution of 2,4,5-trichloropyrimidine (0.15 mL, 1.31 mmol) in 1 mL of DMF was added 4-(dimethylphosphoryl)aniline (0.221 g, 1.31 mmol) and potassium carbonate (0.217 g, 1.57 mmol). The mixture was heated at 110° C. for 4 h. It was basified with saturated sodium bicarbonate solution. The suspension was filtered and washed with ethyl acetate to give the final product (0.15 g, 36% yield). MS/ES+: m/z=316.

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine

To a solution of 5-fluoro-2-nitroanisole (0.5 g, 2.92 mmol) in 3 mL of DMF was added 1-methyl-4-(piperidin)piperazine (0.536 g, 2.92 mmol) and potassium carbonate (0.808, 5.84 mmol). The mixture was heated at 120° C. for 18 h. The mixture was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was purified by chromatography to give final product as yellow solid (0.95 g, 95% yield). MS/ES+: m/z=334.

2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline

The a solution of 1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine (0.3 g, 0.90 mmol) in 10 mL of

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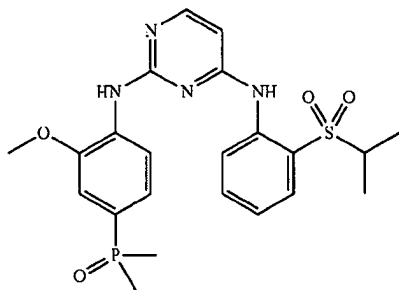
ethanol purged with argon was added 10% Palladium on carbon (0.060 g). The hydrogenation was finished under 30 psi after 4 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.15 g, 88% yield). MS/ES+: $m/z=334$.

5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine

To the compound 2,5-dichloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (0.005 g, 0.16 mmol) in 1 mL of 2-methoxyethanol was added 2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline (0.71 g, 0.16 mmol). The mixture was stirred at 110° C. for 18 h. The mixture was basified with saturated sodium bicarbonate solution and extracted with limited amount of ethyl acetate. The aqueous layer was purified by chromatography to give the final product (0.015 g, 20% yield). MS/ES+: $m/z=583$.

Example 20

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



2-Chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-pyrimidin-4-amine

To a suspension of NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) in 2.0 mL of DMF at room temperature was added 1-amino-2-(isopropylsulphonyl)benzene (0.20 g, 1.0 mmol) as a solid in 3 portions. After 30 minutes of stirring at room temperature, 2,4-dichloropyrimidine (0.15 g, 1.0 mmol) was added as a solution in 1.0 mL DMF. The reaction mixture stirred for 3 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and the solution extracted ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-30% ethyl acetate:heptane) to afford the desired compound as an off-white solid (53 mg, 17% yield). MS/ES+: $m/z=312$.

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

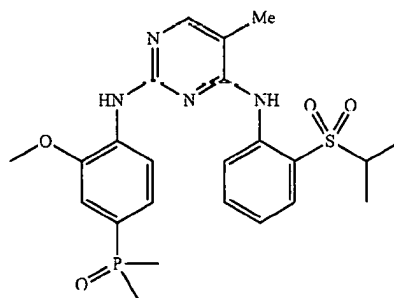
To a solution of 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-pyrimidin-4-amine (0.017 g, 0.054 mmol) in 0.5 mL of 2-methoxyethanol in a vial was added 4-(dimethylphospho-

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ryl)-2-methoxyaniline (0.010 g, 0.044 mmol) as the HCl salt. The vial was sealed and the reaction was heated at 90° C. for 16 h. The reaction was quenched with 1N NaOH solution and the solution extracted ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired compound (15 mg, 72% yield). MS/ES+: $m/z=475$.

Example 21

N²-[4-(Dimethylphosphoryl)-2-methoxyphenyl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



2-Chloro-5-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]-pyrimidin-4-amine

To a suspension of NaH (60% dispersion in mineral oil, 40.0 mg, 1.00 mmol) in 2 mL of DMF at room temperature was added 1-amino-2-(isopropylsulphonyl)benzene (0.20 g, 1.0 mmol) as a solid in 3 portions. After 30 minutes of stirring at room temperature, 2,4-dichloro-5-methylpyrimidine (0.17 g, 1.0 mmol) was added as a solution in 1 mL DMF. The reaction mixture stirred for 3 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and the solution extracted ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-30% ethyl acetate:heptane) to afford the desired compound as an off-white solid (78 mg, 24% yield). MS/ES+: $m/z=326$.

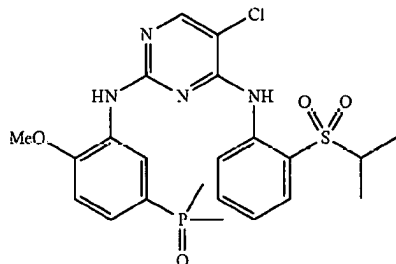
N²-[4-(Dimethylphosphoryl)-2-methoxyphenyl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2-chloro-5-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]-pyrimidin-4-amine (0.035 g, 0.11 mmol) in 1 mL of 2-methoxyethanol in a vial was added 4-(dimethylphosphoryl)-2-methoxyaniline (0.020 g, 0.085 mmol) as the HCl salt. The vial was sealed and the reaction was heated at 90° C. for 16 h. The reaction was quenched with 1N NaOH solution and the solution extracted ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired compound (12 mg, 29% yield). MS/ES+: $m/z=489$.

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Example 22

5-Chloro-N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



5-(Dimethylphosphoryl)-2-methoxyaniline

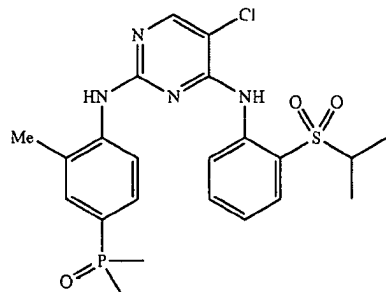
To a solution of 5-bromo-2-methoxyaniline (0.404 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.365 g, 85% yield).

5-Chloro-N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as prepared in Example 17: 0.077 g, 0.22 mmol) in 1.5 mL of 2-methoxyethanol was added 5-(dimethylphosphoryl)-2-methoxyaniline (0.050 g, 0.21 mmol) as its hydrochloride salt. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by prep-HPLC to afford the final compound (52 mg, 48% yield). MS/ES+: m/z=509.

Example 23

5-Chloro-N²-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



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4-(Dimethylphosphoryl)-2-methylaniline

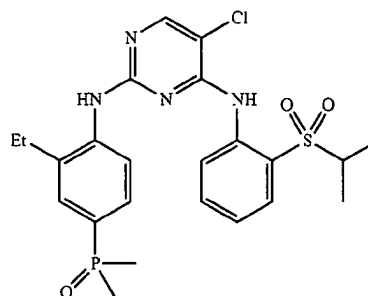
To a solution of 4-bromo-2-methylaniline (0.372 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.313 g, 85% yield).

5-Chloro-N²-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as prepared in Example 17: 0.083 g, 0.24 mmol) in 1.5 mL of 2-methoxyethanol was added 4-(dimethylphosphoryl)-2-methylaniline (0.050 g, 0.23 mmol) as its hydrochloride salt. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by prep-HPLC to afford the final compound (20 mg, 18% yield). MS/ES+: m/z=493.

Example 24

5-Chloro-N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



4-(Dimethylphosphoryl)-2-ethylaniline

To a solution of 4-bromo-2-ethylaniline (0.400 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.308 g, 78% yield).

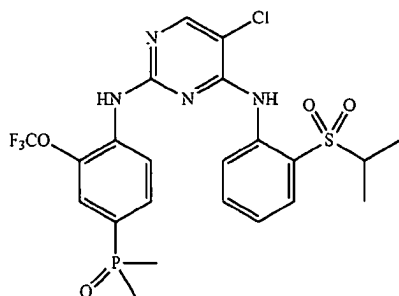
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5-Chloro-N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as prepared in Example 17: 0.079 g, 0.22 mmol) in 1.5 mL of 2-methoxyethanol was added 4-(dimethylphosphoryl)-2-ethylphenyl (0.050 g, 0.21 mmol) as its hydrochloride salt. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by prep-HPLC to afford the final compound (43 mg, 40% yield). MS/ES+: m/z=507.

Example 25

5-Chloro-N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



4-(Dimethylphosphoryl)-2-(trifluoromethoxy)aniline

To a solution of 4-iodo-2-(trifluoromethoxy)aniline (0.606 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) and acidified with HCl in methanol to afford the desired product as its hydrochloride salt (0.573 g, 98% yield).

5-Chloro-N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

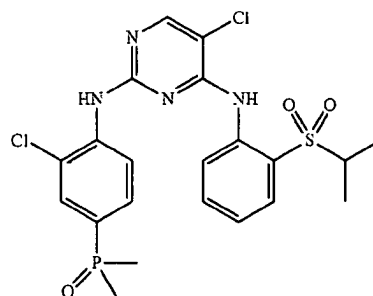
To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as prepared in Example 17: 0.040 g, 0.12 mmol) in 1 mL of 2-methoxyethanol was added 4-(dimethylphosphoryl)-2-(trifluoromethoxy)aniline (0.035 g, 0.12 mmol) as its hydrochloride salt. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl

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acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by prep-HPLC to afford the final compound (5.8 mg, 9% yield). MS/ES+: m/z=563.

Example 26

5-Chloro-N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



2-Chloro-4-(dimethylphosphoryl)aniline

To a solution of 2-chloro-4-iodoaniline (0.507 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.340 g, 83% yield).

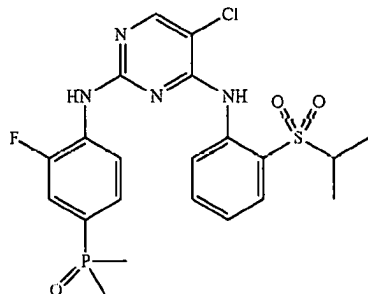
5-Chloro-N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (0.040 g, 0.12 mmol) in 1 mL of 2-methoxyethanol was added 2-chloro-4-(dimethylphosphoryl)aniline (as prepared in Example 17: 0.025 g, 0.12 mmol) and 49 µL of 2.5 M HCl in ethanol. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by prep-HPLC to afford the final compound (5.9 mg, 10% yield). MS/ES+: m/z=513.

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Example 27

5-Chloro-N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



4-(Dimethylphosphoryl)-2-fluoroaniline

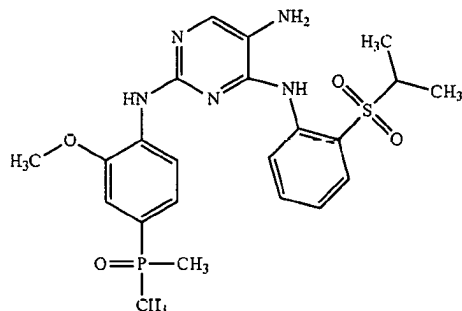
To a solution of 4-bromo-2-fluoroaniline (0.380 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (73.5 mg, 20% yield).

5-Chloro-N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as prepared in Example 17; 0.040 g, 0.12 mmol) in 1 mL of 2-methoxyethanol was added 4-(dimethylphosphoryl)-2-fluoroaniline (0.023 g, 0.12 mmol) and 49 µL of 2.5 M HCl in ethanol. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by prep-HPLC to afford the final compound (9.0 mg, 22% yield). MS/ES+: m/z=497.

Example 28

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4,5-triamine

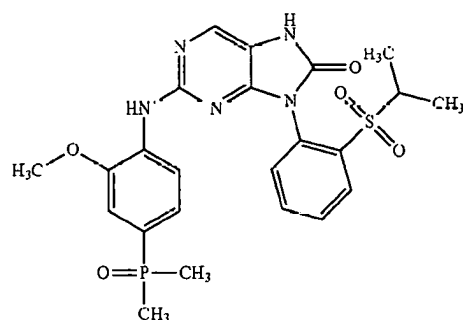


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A suspension of N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-nitro-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine (461 mg, 0.89 mmol) in Ethanol was added 184 mg of 10% Pd on carbon. The reaction mixture was stirred at room temperature overnight and filtered through celite. The filtrate was concentrated under reduced pressure to yield the crude product. The crude product was purified by silica gel chromatography with 10% Methanol in DCM to yield N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4,5-triamine as a solid. MS ES+: m/z=490

Example 29

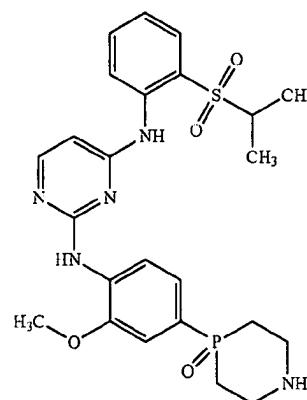
2-{[4-(dimethylphosphoryl)-2-methoxyphenyl]amino}-9-[2-(propan-2-ylsulfonyl)phenyl]-7,9-dihydro-8H-purin-8-one



To a solution of N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4,5-triamine (as prepared in Example 28; 40 mg, 0.082 mmol) in THF was added N,N'-Carbonyldiimidazole (40 mg, 0.25 mmol). The solution was stirred at room temperature overnight. The solution was concentrated under reduced pressure and diluted with water and extracted with Ethyl Acetate. The combined organic layer was washed with brine and dried over Magnesium Sulfate. The organic layer was concentrated under reduced pressure and the residue was purified by RP Prep-HPLC to obtain the desired product as an off white solid. MS/ES+: m/z=516

Example 30

N²-[2-methoxy-4-(4-oxido-1,4-azaphosphinan-4-yl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



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(3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide

To a solution of 5-chloro-2-nitroanisole (1.00 g, 5.33 mmol) in 20 mL DMF was added diethyl phosphite (0.809 g, 5.86 mmol), palladium acetate (0.060 g, 0.27 mmol), Xantphos (0.185 g, 0.320 mmol), and potassium phosphate (1.24 g, 5.86 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-45% ethyl acetate:heptane) to afford the desired product (0.504 g, 33% yield).

(3-methoxy-4-nitrophenyl)phosphonic dichloride

To a solution of (3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide (4.54 g, 15.7 mmol) in 1.2 mL DMF was added thionyl chloride (5.7 mL, 78.5 mmol). The reaction flask was equipped with a reflux condenser and the mixture was heated to reflux. After 2 h at reflux, the reaction was cooled to rt and concentrated in vacuo. The crude oil was redissolved in CH₂Cl₂ and heptane was added to precipitate the desired compound. The clear solution was decanted and the precipitate was collected and dried to afford the desired compound as a white solid (1.39 g, 33% yield).

Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide

To a solution of (3-methoxy-4-nitrophenyl)phosphonic dichloride (1.39 g, 5.15 mmol) in 15 mL THF at -78° C. under nitrogen was slowly added vinylmagnesium bromide (10.3 mL, 1.0 M in THF). After the addition was complete, the reaction stirred at -78° C. for an additional hour. The cold reaction mixture was quenched by the addition of saturated NH₄Cl (20 mL) and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with 1 M NaOH, brine, and dried over MgSO₄. The organic extracts were filtered and concentrated to provide the desired compound (0.982 g, 75%).

1-benzyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide

diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.480 g, 1.90 mmol) and benzylamine (0.23 mL, 2.08 mmol) were dissolved in 50% aqueous TBAF (6 mL) and heated to 105° C. under nitrogen. After one hour, another portion of benzylamine was added to the reaction mixture. The reaction mixture was refluxed for an additional 2 h, and then cooled to rt. The reaction mixture was partitioned between saturated aqueous NaHCO₃ and CH₂Cl₂. The aqueous phase was washed once with CH₂Cl₂ and the organic layers were combined. The organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (0-5% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.449 g, 66% yield).

4-(1-benzyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline

To a solution of 1-benzyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide (0.224 g, 0.622 mmol) in 0.6 mL 4:1 ethanol:water was added iron powder (0.348 g, 6.22 mmol) and 0.30 mL ethanolic HCl (2.5 M). The reaction vessel was sealed and was heated to 95° C. for 1 h. The

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reaction mixture was cooled to rt, filtered, and concentrated. The crude residue was purified by silica gel chromatography (0-5% 7N ammonia in methanol:dichloromethane) to afford the desired product (86.1 mg, 42% yield).

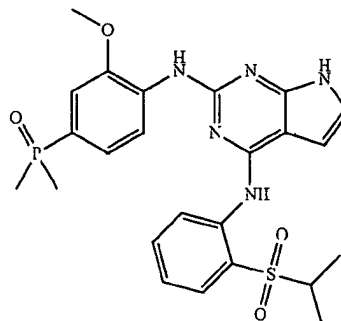
N²-[4-(1-benzyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]-5-chloro-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (47.3 mg, 0.137 mmol) in 1.5 mL of 2-methoxyethanol was added 4-(1-benzyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline (43.0 mg, 0.13 mmol) and ethanolic HCl (0.10 mL, 2.5 M). The mixture was heated in a sealed vial at 90° C. for 16 h. The reaction was then heated at 100° C. for an additional 2 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-12% 7N ammonia in methanol:dichloromethane) to afford the desired product (43.0 mg, 52% yield).

N²-[4-methoxy-4-(4-oxido-1,4-azaphosphinan-4-yl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

A flask was charged with N²-[4-(1-benzyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]-5-chloro-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine (40.0 mg, 0.0625 mmol) and 10% Pd-C (40.0 mg). The flask was evacuated and filled with nitrogen. Anhydrous methanol (2 mL) was added to the flask and the flask was equipped with a reflux condenser with a nitrogen inlet. Ammonium formate (31.5 mg, 0.500 mmol) was added in one portion at room temperature. The resulting mixture was stirred at reflux for 3 h. The reaction was filtered through a Celite pad and the Celite was washed with 2x5 mL methanol. The combined filtrate and washing was evaporated in vacuo. The crude residue was purified by prep-HPLC to afford the final compound (13.6 mg, 42% yield). MS/ES+: m/z=516.

Example 31

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

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2,4-dichloro-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidine

To a suspension of NaH (119 mg, 60% in oil, 2.98 mmol) in DMF (5 mL) was added 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (400 mg, 2.13 mmol) at 0° C. The resulting mixture was stirred for 30 min before 2-(trimethylsilyl)ethoxymethyl chloride (0.42 mL, 1.1 eq) was added. The mixture was then warmed up to room temperature and stirred for 1 hr. Water was added to quench the reaction. Extraction with CH_2Cl_2 followed by drying combined organic layers, evaporation, and chromatography on silica gel (20% EtOAc in heptane as eluent) gave the desired product in 84% yield (570 mg).

2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine

To a solution of 1-amino-2-(isopropylsulfonyl)benzene (199 mg, 1 mmol) in 2 mL of DMF was added NaH (60% in oil, 44 mg, 1.1 mmol) in one portion at 0° C. After the reaction mixture was stirred for 20 min, 2,4-dichloro-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidine (317 mg, 1 mmol) was added at 0° C. The reaction mixture was then warmed up to room temperature and stirred for additional 2 h. The reaction was quenched with water. Extraction with EtOAc followed by silica gel column chromatography (20% EtOAc in heptane) gave the desired product (202 mg, 42% yield). MS/ES+: $m/z=481$.

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

To a microwave reaction tube was charged with 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (180 mg, 0.374 mmol), 4-(dimethylphosphoryl)-2-methoxyaniline hydrochloride (105 mg, 0.45 mmol), $\text{Pd}(\text{dppf})_2$ (34 mg, 0.0374 mmol), Xantphos (26 mg, 0.045 mmol), and t-BuONa (129 mg, 1.346 mmol). This mixture was degassed via 3-cycle of vacuum and re-fill with N_2 . Anhydrous 1,4-dioxane (2 mL from sure-seal bottle) was added and the reaction was then run under microwave irradiation at 140° C. for 20 min. Water and EtOAc was added to facilitate extraction. Chromatography on silica gel (10% MeOH in CH_2Cl_2 as eluent) gave the desired product in 54% yield (130 mg). MS/ES+: $m/z=644$.

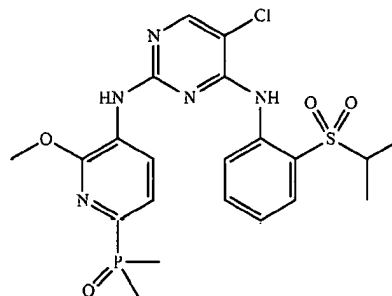
N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

To a solution of compound N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine in THF (1 mL) was added tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 3 mL) and ethylenediamine (0.1 mL). The solution was heated at 60° C. for 24 hrs. About 40% conversion was observed by HPLC monitoring. Volatile components were removed on rotavap and the residue was subjected to prep-HPLC purification. The desired product was determined by NMR to be contaminated

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with TBAF, which was removed by water wash (4 times). Evaporation of EtOAc gave the pure compound (14 mg). MS/ES+: $m/z=514$.

Example 32

5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

6-(Dimethylphosphoryl)-2-methoxypyridin-3-ylamine

To a solution of 6-bromo-2-methoxypyridin-3-ylamine (0.203 g, 1.00 mmol) in 4 mL DMF was added dimethylphosphine oxide (0.171 g, 1.10 mmol), palladium acetate (11.0 mg, 0.0490 mmol), XANTPHOS (35.0 mg, 0.0600 mmol), and potassium phosphate (0.233 g, 1.10 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (77.2 mg, 39% yield).

2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine

To a solution of 1-Amino-2-(isopropylsulfonyl)benzene (0.955 g, 4.80 mmol) in 2 mL of DMF at 0° C. was added NaH (60% in oil, 0.349 g, 8.72 mmol) in one portion. After stirring for 20 min, 2,4,5-trichloropyrimidine was added. The mixture was stirred at 0° C. for 30 minutes, and then at room temperature for 2 h. After quenching with saturated ammonium chloride solution, the mixture was poured in water and ethyl acetate mixture. Yellow suspension was filtered as final product (0.3 g, 20% yield). MS/ES+: $m/z=346$.

5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

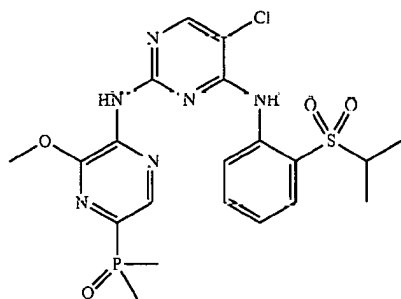
To a solution of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (86.0 mg, 0.250 mmol) in 1 mL of 2-methoxyethanol was added 6-(dimethylphosphoryl)-2-methoxypyridin-3-ylamine (50.0 mg, 0.250 mmol) and 0.15 mL of 2.5 M HCl in ethanol. The mixture was heated in a sealed tube at 90° C. for 16 h. The mixture was basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chro-

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matography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (16.7 mg, 22% yield). MS/ES+: m/z =510.

Example 33

5-chloro-N²-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine

To a solution of 5-bromo-3-methoxypyrazin-3-ylamine (0.204 g, 1.00 mmol) in 4 mL DMF was added dimethylphosphine oxide (0.171 g, 1.10 mmol), palladium acetate (11.0 mg, 0.0490 mmol), XANTPHOS (35.0 mg, 0.0600 mmol), and potassium phosphate (0.233 g, 1.10 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (126 mg, 63% yield).

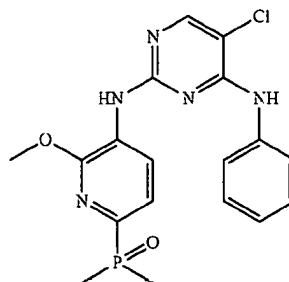
5-chloro-N²-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a mixture of 2,5-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (prepared in Example 32: 0.120 g, 0.348 mmol) and 5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine (70.0 mg, 0.348 mmol) was added tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (17.6 mg, 0.017 mmol), XANTPHOS (23.3 mg, 0.040 mmol), and cesium carbonate (0.228 g, 0.700 mmol), and dioxane (3.5 mL). The mixture was sealed and heated at 120° C. After 16 h, the reaction mixture was cooled to rt and concentrated. The crude residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (11.4 mg, 6% yield). MS/ES+: m/z =511.

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Example 34

5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-phenylpyrimidine-2,4-diamine



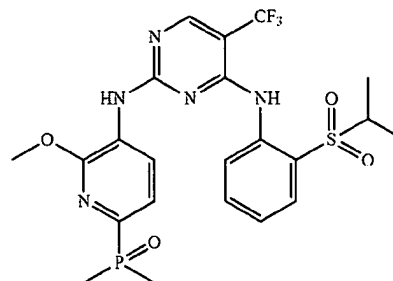
This compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-phenylpyrimidin-4-amine with 6-(Dimethylphosphoryl)-2-methoxypyridin-3-ylamine (prepared in Example 32)

2,5-dichloro-N-phenylpyrimidin-4-amine

To a solution of Aniline (205 mg, 2.2 mmol) and 2,4,5-Trichloropyrimidine (500 mg, 2.7 mmol) in 5 mL of Ethanol, was added 500 mg of Potassium carbonate. The reaction mixture was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography with 10% Ethyl Acetate in Heptane to yield the desired product as an oil (370 mg, 70% yield).

Example 35

N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine



4-chloro-2-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-(trifluoromethyl)pyrimidine

A suspension of 6-(dimethylphosphoryl)-2-methoxypyridin-3-ylamine (prepared in Example 32: 2.2 mmol) in 15 mL of N,N-Dimethylacetamide and 3.6 mL of Diisopropylethyl-

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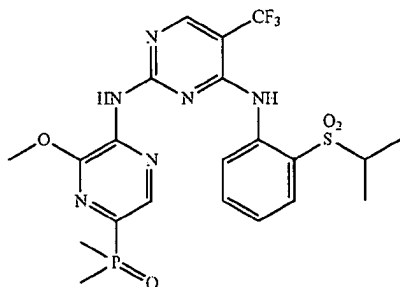
amine, is allowed to stirred at room temperature for 15 minutes until a clear solution is obtained. 2,4-Dichloro-5-(trifluoromethyl)pyrimidine (5.7 g, 2.6 mmol) is added in four portions over 5 minutes. The reaction mixture is stirred at 60 degrees for 1 hour. The reaction mixture is cooled to room temperature and filtered to obtain a white solid. The white solid is washed with 50 mL of water three times and followed by 50 mL of Ethyl ether three times. The white solid is dried under vacuum to yield 4-chloro-2-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-(trifluoromethyl)pyrimidine

N^2 -[4-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^4 -[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine

To a solution of 4-chloro-2-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-(trifluoromethyl)pyrimidine (0.072 mmol) in 1.5 mL of ethanol is added 10 μ L of triethylamine and 1-Amino-2-(isopropylsulphonyl)benzene (0.072 mmol). The mixture is microwave at 120 degrees for 20 minutes. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to generate the desired compound.

Example 36

N^2 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^4 -[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine



4-chloro-2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-5-(trifluoromethyl)pyrimidine

A suspension of 5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine (prepared in Example 33: 2.2 mmol) in 15 mL of N,N-Dimethylacetamide and 3.6 mL of Diisopropylethylamine, is allowed to stirred at room temperature for 15 minutes until a clear solution is obtained. 2,4-Dichloro-5-(trifluoromethyl)pyrimidine (5.7 g, 2.6 mmol) is added in four portions over 5 minutes. The reaction mixture is stirred at 60 degrees for 1 hour. The reaction mixture is cooled to room temperature and filtered to obtain a white solid. The white solid is washed with 50 mL of water three times and followed by 50 mL of Ethyl ether three times. The white solid is dried under vacuum to yield 4-chloro-2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-5-(trifluoromethyl)pyrimidine.

N^2 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^4 -[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine

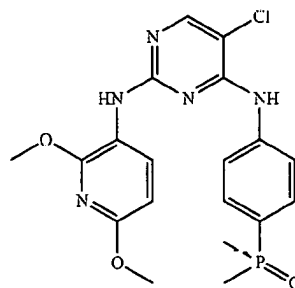
To a solution of 4-chloro-2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-5-(trifluoromethyl)pyrimidine (0.072 mmol) in 1.5 mL of ethanol is added 10 μ L of triethylamine

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and 1-Amino-2-(isopropylsulphonyl)benzene (0.072 mmol). The mixture is microwave at 120 degrees for 20 minutes. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC (Waters Sunfire C18 column with ACN/water mobile phases) to generate the desired compound.

Example 37

5-chloro- N^2 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^4 -[4-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine



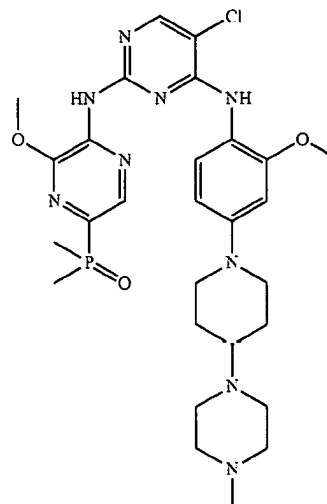
This compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine with 2,6-Dimethoxypyridin-3-amine.

2,5-dichloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine

To a solution of 2,4,5-trichloropyrimidine (0.15 mL, 1.31 mmol) in 1 mL of DMF was added 4-(dimethylphosphoryl)aniline (0.221 g, 1.31 mmol) and potassium carbonate (0.217 g, 1.57 mmol). The mixture was heated at 110° C. for 4 h. It was basified with saturated sodium bicarbonate solution. The suspension was filtered and washed with ethyl acetate to give the final product (0.15 g, 36% yield). MS/ES+: m/z =316.

Example 38

5-chloro- N^2 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^4 -[2-methoxy-4-[4-(4-methylpiperazin-1-yl)phenyl]phenyl]pyrimidine-2,4-diamine



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This compound can be prepared as in Example 32 by reacting 2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline with 2,4,5-trichloropyrimidine to generate 2,5-dichloro-N-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidin-4-amine. 2,5-dichloro-N-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidin-4-amine is then reacted with 5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine (prepared in Example 33) according to the procedure described in Example 32.

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine

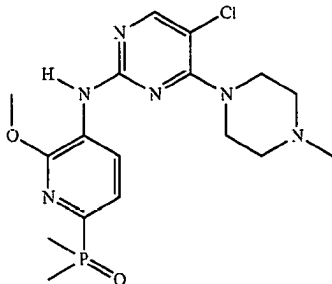
To a solution of 5-fluoro-2-nitroanisole (0.5 g, 2.92 mmol) in 3 mL of DMF was added 1-methyl-4-(piperidin)piperazine (0.536 g, 2.92 mmol) and potassium carbonate (0.808, 5.84 mmol). The mixture was heated at 120° C. for 18 h. The mixture was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was purified by chromatography to give final product as yellow solid (0.95 g, 95% yield). MS/ES+: m/z=334.

2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline

The a solution of 1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine (0.3 g, 0.90 mmol) in 10 mL of ethanol purged with argon was added 10% Palladium on carbon (0.060 g). The hydrogenation was finished under 30 psi after 4 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.15 g, 88% yield). MS/ES+: m/z=334.

Example 39

5-chloro-N-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-4-(4-methylpiperazin-1-yl)pyrimidin-2-amine



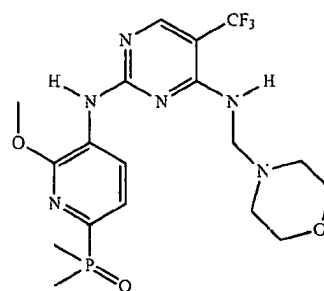
This compound can be prepared by reacting 2,4,5-trichloropyrimidine with 1-Methyl piperazine as described in Example 32 to generate 2,5-dichloro-4-(4-methylpiperazin-1-yl)pyrimidine. 2,5-dichloro-4-(4-methylpiperazin-1-yl)

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pyrimidine is then reacted with 6-(dimethylphosphoryl)-2-methoxypyridin-3-ylamine (prepared in Example 32) as described in Example 32.

Example 40

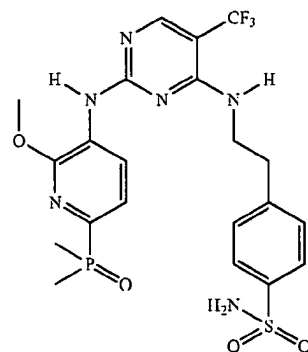
N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-(morpholin-4-ylmethyl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



This compound can be prepared by reacting 1-(morpholin-4-yl)methanamine with 4-chloro-2-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-(trifluoromethyl)pyrimidine as described in Example 35.

Example 41

4-(2-{[2-{[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}ethyl)benzenesulfonamide

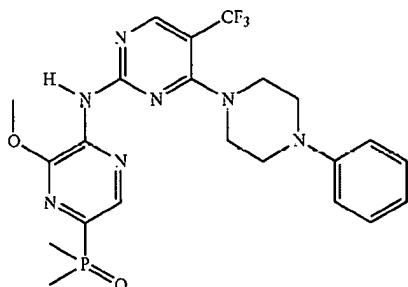


This compound can be prepared by reacting 4-(2-aminoethyl)benzene-sulfonamide with 4-chloro-2-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-(trifluoromethyl)pyrimidine as described in Example 35.

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Example 42

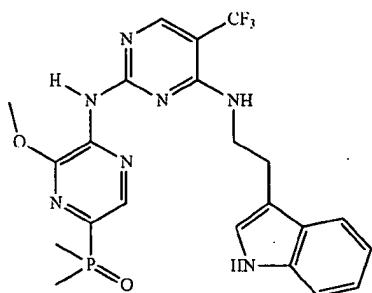
2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-4-(4-phenylpiperazin-1-yl)-5-(trifluoromethyl)pyrimidine



This compound can be prepared by reacting 1-Phenylpiperazine with 4-chloro-2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-5-(trifluoromethyl)pyrimidine as described in Example 36.

Example 43

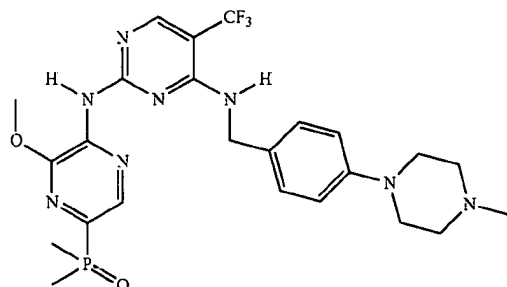
2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N-[2-(1H-indol-3-yl)ethyl]-5-(trifluoromethyl)pyrimidin-4-amine



This compound can be prepared by reacting tryptamine with 4-chloro-2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-5-(trifluoromethyl)pyrimidine as described in Example 36.

Example 44

N²-[4-(dimethylphosphoryl)phenyl]-N⁴-[4-(4-methylpiperazin-1-yl)benzyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine

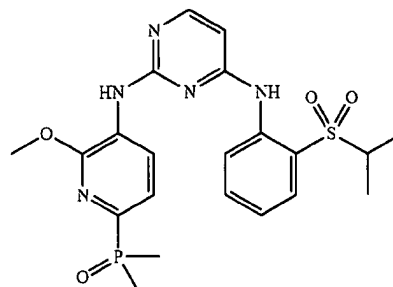


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This compound can be prepared by reacting 4-(4-methylpiperazine)-benzylamine with 4-chloro-2-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-5-(trifluoromethyl)pyrimidine as described in Example 36.

Example 45

N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



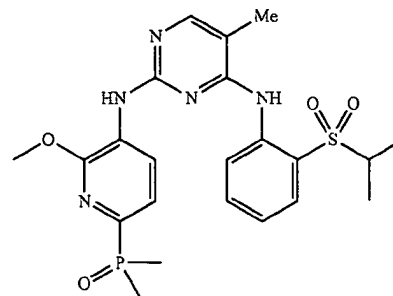
This compound can be prepared as in Example 32 by reacting 2-Chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine with 6-(dimethylphosphoryl)-2-methoxypyridin-3-ylamine (prepared in Example 32).

2-Chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine

To a suspension of NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) in 2.0 mL of DMF at room temperature was added 1-amino-2-(isopropylsulfonyl)benzene (0.20 g, 1.0 mmol) as a solid in 3 portions. After 30 minutes of stirring at room temperature, 2,4-dichloropyrimidine (0.15 g, 1.0 mmol) was added as a solution in 1.0 mL DMF. The reaction mixture stirred for 3 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and the solution extracted ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-30% ethyl acetate:heptane) to afford the desired compound as an off-white solid (53 mg, 17% yield). MS/ES+: m/z=312.

Example 46

N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine



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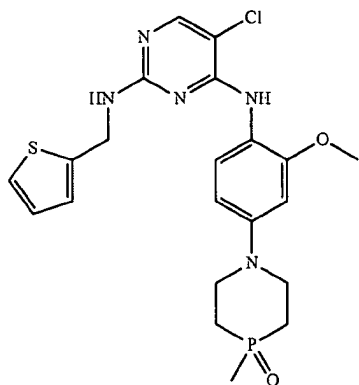
This compound can be prepared as in Example 32 by reacting 2-Chloro-5-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]-pyrimidin-4-amine with 6-(dimethylphosphoryl)-2-methoxypyridin-3-ylamine (prepared in Example 32).

2-Chloro-5-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]-pyrimidin-4-amine

To a suspension of NaH (60% dispersion in mineral oil, 40.0 mg, 1.00 mmol) in 2 mL of DMF at room temperature was added 1-amino-2-(isopropylsulfonyl)benzene (0.20 g, 1.0 mmol) as a solid in 3 portions. After 30 minutes of stirring at room temperature, 2,4-dichloro-5-methylpyrimidine (0.17 g, 1.0 mmol) was added as a solution in 1 mL DMF. The reaction mixture stirred for 3 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and the solution extracted ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-30% ethyl acetate:heptane) to afford the desired compound as an off-white solid (78 mg, 24% yield). MS/ES+: m/z=326.

Example 47

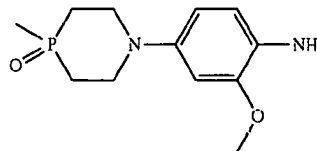
5-chloro-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N²-(thiophen-2-ylmethyl)pyrimidine-2,4-diamine



The compound can be prepared as in Example 32 by reacting 2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline with 2,4,5-trichloropyrimidine generating 2,5-dichloro-N-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidin-4-amine. 2,5-dichloro-N-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidin-4-amine is then reacted with 1-(thiophen-2-yl)methanamine as described in Example 32.

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2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline



1-benzyl-4-methyl-1,4-azaphosphinane 4-oxide

To a solution of methylphosphonic dichloride (10.0 g, 75.2 mmol) in CH₂Cl₂ at -78° C., was added vinylmagnesium bromide (175 mL, 1.0 M in THF) via addition funnel over 4 h. The solution was warmed to 0° C. and quenched with a minimum amount of saturated NH₄Cl. The mixture was filtered through a pad of silica gel and silica was extracted with 10% 7N ammonia in methanol:dichloromethane. The solution was concentrated under reduced pressure to afford methyl divinyl phosphine oxide as a viscous, yellow oil that was used without purification.

A solution of methyl divinyl phosphine oxide (1.16 g, 10.0 mmol) and benzylamine (1.20 mL, 11.0 mmol) in 1:1 THF/water (25 mL) was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford 1-benzyl-4-methyl-[1,4]azaphosphinane-4-oxide as a white solid (1.57 g, 70% yield).

4-methyl-[1,4]azaphosphinane-4-oxide

A flask was charged with 1-benzyl-4-methyl-[1,4]azaphosphinane-4-oxide (1.00 g, 4.47 mmol) and 10% Pd/C (100 mg). The flask was evacuated and filled with nitrogen. Anhydrous methanol (18 mL) was added to the flask and the flask was equipped with a reflux condenser with a nitrogen inlet. Ammonium formate (2.25 g, 35.8 mmol) was added in one portion at room temperature. The resulting mixture was stirred at reflux for 2 h. The reaction was filtered through a Celite pad and the Celite was washed with 2x5 mL methanol. The combined filtrate and washing was evaporated in vacuo. The crude residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford 4-methyl-[1,4]azaphosphinane-4-oxide as a yellow gel (0.589 g, 99% yield).

1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide

A mixture of 4-methyl-[1,4]azaphosphinane-4-oxide (133 mg, 1.00 mmol), 5-fluoro-2-nitroanisole (340 mg, 2.00 mmol), K₂CO₃ (345 mg, 2.50 mmol), and DMF (5 mL) was heated to 50° C. After 2 h, the reaction mixture was concentrated and purified by silica gel chromatography (0-5% 7N ammonia in methanol:dichloromethane) to afford 1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide as a bright yellow solid (272 mg, 96% yield).

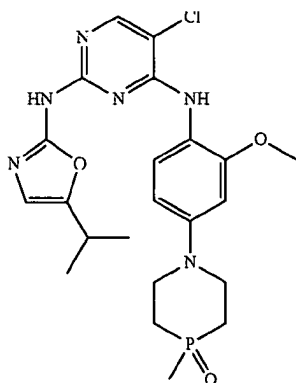
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2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline

To a pressure vessel was added 1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide (272 mg, 0.960 mmol), ethanol (5 mL), and 10% Pd/C (50 mg). The vessel was connected to a Parr apparatus, evacuated, and refilled with nitrogen. The vessel was then evacuated and filled with hydrogen gas to a pressure of 50 psi. The reaction mixture was shaken under 50 psi for 4 h. The mixture was filtered through Celite to a flask containing HCl in ethanol. Concentration of the filtrate afforded 2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline as a gray solid (211 mg, 87% yield).

Example 48

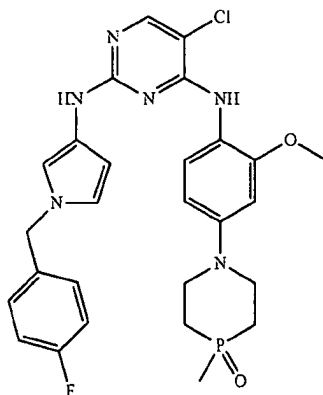
5-chloro-N²-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N²-[5-(propan-2-yl)-1,3-oxazol-2-yl]pyrimidine-2,4-diamine



The compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidin-4-amine (as described in Example 47) with 5-(propan-2-yl)-1,3-oxazol-2-amine.

Example 49

5-chloro-N²-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidine-2,4-diamine



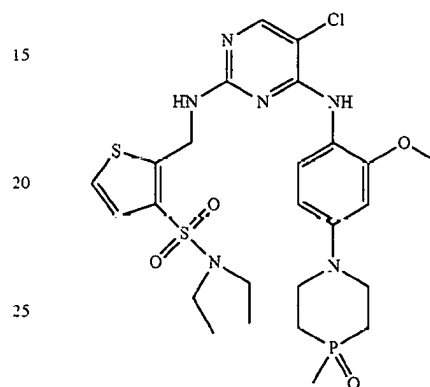
The compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[2-methoxy-4-(4-methyl-4-oxido-1,4-

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azaphosphinan-1-yl)phenyl]pyrimidin-4-amine (as described in Example 47) with 1-(4-fluorobenzyl)-1H-pyrrol-3-amine.

Example 50

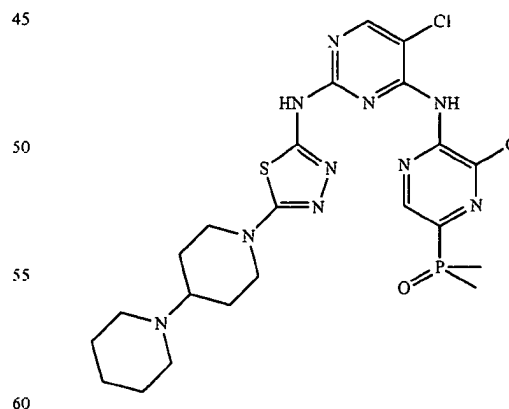
2-[[[(5-chloro-4-[[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]amino]pyrimidin-2-yl)amino]methyl]-N,N-diethylthiophene-3-sulfonamide



The compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidin-4-amine (as described in Example 47) with 2-(aminomethyl)-N,N-diethylthiophene-3-sulfonamide.

Example 51

N²-[5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-yl]-5-chloro-N-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]pyrimidine-2,4-diamine



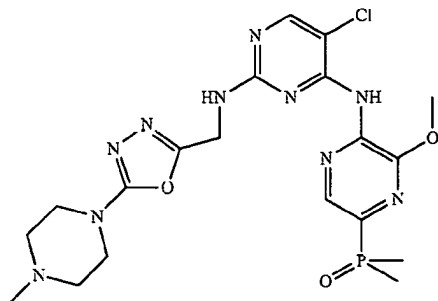
This compound can be prepared as in Example 32 by reacting 5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine (prepared in example 33) with 2,4,5-trichloropyrimidine to generate 2,5-dichloro-N-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]pyrimidin-4-amine. 2,5-dichloro-N-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]

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pyrimidin-4-amine is then reacted with 5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-amine according to the procedure described in Example 321.

Example 52

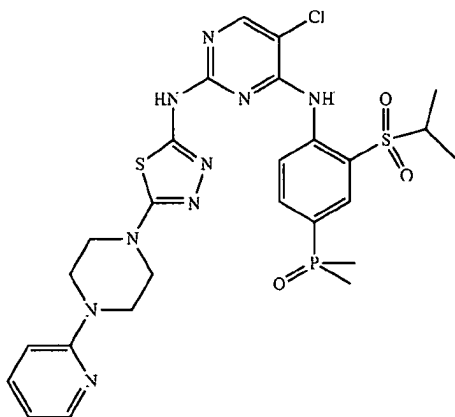
5-chloro-N⁴-[5-(dimethylphosphoryl)-3-methoxy-pyrazin-2-yl]-N²-{[5-(4-methylpiperazin-1-yl)-1,3,4-oxadiazol-2-yl]methyl}pyrimidine-2,4-diamine



This compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[5-(dimethylphosphoryl)-3-methoxy-pyrazin-2-yl]pyrimidin-4-amine (as described in Example 51) with 1-[5-(4-methylpiperazin-1-yl)-1,3,4-oxadiazol-2-yl]methanamine.

Example 53

5-chloro-N⁴-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N²-{5-[4-(pyridin-2-yl)piperazin-1-yl]-1,3,4-oxadiazol-2-yl}pyrimidine-2,4-diamine

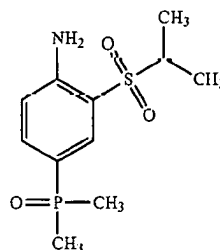


This compound can be prepared as in Example 32 by reacting 4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline with 2,4,5-trichloropyrimidine to generate 2,5-dichloro-N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine. 2,5-dichloro-N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine is then reacted with 5-[4-(pyridin-2-yl)

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piperazin-1-yl]-1,3,4-oxadiazol-2-amine according to the procedure described in Example 32.

4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline



4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene

At 0 degree, to a stirring solution of 4-Bromo-2-Fluoroaniline (2.0 g, 9.1 mmol) in DCM was added Sodium Isopropoxide (2.0 g, 20 mmol) in two portions. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through a syringe filter. The product was isolated by prep-HPLC (water/Acetonitrile) as a bright yellow solid (0.8 g, 2.9 mmol, 32% yield).

4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene

To a stirring solution of 4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene (0.8 g, 2.9 mmol) in Acetic Acid (10 ml) was added Hydrogen Peroxide (30% aqueous solution, 0.6 mL, 5.8 mmol). The reaction mixture was heated to 110 degrees C. for 2 hours in oil bath. The reaction mixture was treated with saturated Sodium Sulfide aqueous solution and basified with saturated sodium bicarbonate solution. The mixture was extracted with Ethyl Acetate and the combined organic layers were dried over sodium sulfate. The organic solvent was removed under reduced pressure and the residue was used for the next step reaction without further purification.

Dimethyl[4-nitro-3-(propan-2-ylsulfonyl)phenyl]phosphane oxide

To a stirring solution of 4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene (0.44 g, 1.6 mmol) and Dimethyl Phosphine oxide (0.15 g, 1.9 mmol) in 1 mL of DMF, was added Potassium Phosphate (0.37 g, 1.8 mmol), Pd(OAc)₂ (18 mg, 0.08 mmol), Xanphos (55 mg, 0.10 mmol). The reaction mixture was stirred at 110 degrees C. overnight. The reaction mixture was cooled to room temperature and filtered through celite. The desired product was isolated through prep-HPLC to yield a brownish yellow solid (0.24 g, 55% yield).

4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline

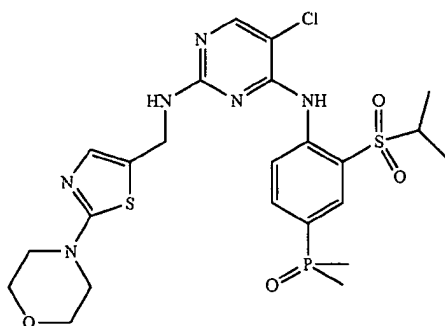
To a solution of dimethyl[4-nitro-3-(propan-2-ylsulfonyl)phenyl]phosphane oxide (0.24 g, 0.88 mmol) in Ethanol was added Pd on carbon (10% w/w, 24 mg) and stirred under hydrogen overnight. The reaction mixture was filtered and the

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organic solvent was removed under reduced pressure. The residue was purified by prep-HPLC to yield 100 mg of desired product (50% yield).

Example 54

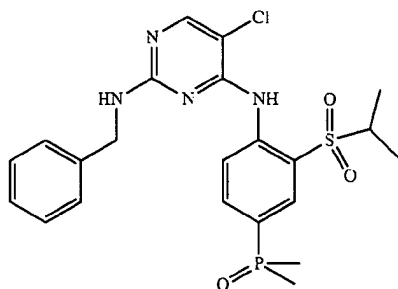
5-chloro-N²-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N⁴-{[2-(morpholin-4-yl)-1,3-thiazol-4-yl]methyl}pyrimidine-2,4-diamine



This compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as described in Example 53) with 1-[2-(morpholin-4-yl)-1,3-thiazol-4-yl]methanamine.

Example 55

N²-benzyl-5-chloro-N⁴-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

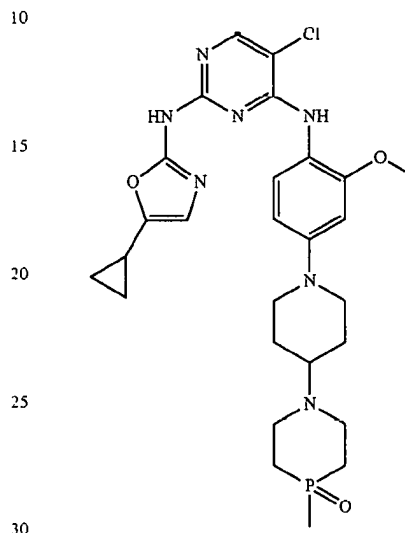


This compound can be prepared as in Example 32 by reacting 2,5-dichloro-N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (as described in Example 53) with benzylamine.

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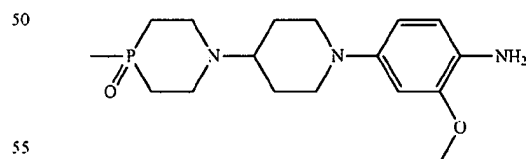
Example 56

5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine



This compound can be prepared as in Example 32 by reacting 2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline with 2,4,5-trichloropyrimidine to generate 2,5-dichloro-N-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}pyrimidin-4-amine. 2,5-dichloro-N-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}pyrimidin-4-amine is then reacted with 5-cyclopropyl-1,3-oxazol-2-amine according to the procedure described in Example 32.

2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline



tert-butyl 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidine-1-carboxylate

A solution of methyl divinyl phosphine oxide (140 mg, 1.21 mmol) and 1-Boc-4-aminopiperidine (265 mg, 1.33 mmol) in 1:1 THF/water (3 ml) was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0-10% 7N

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ammonia in methanol:dichloromethane) to afford the desired compound as a white solid (178 mg, 38% yield).

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methyl-1,4-azaphosphinane 4-oxide

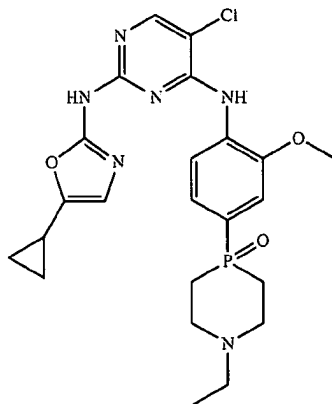
To a stirring solution of tert-butyl 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidine-1-carboxylate (178 mg, 0.563 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.5 mL). After 20 min, the solution was concentrated and the resulting residue was redissolved in DMF (2 mL). Potassium carbonate (160 mg, 1.16 mmol) was added portionwise to the stirring solution followed by 5-fluoro-2-nitroanisole (158 mg, 0.930 mmol). The reaction mixture was heated to 50° C. After 2 h, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the compound as a bright yellow solid (176 mg, 86% yield).

2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline

To a pressure vessel was added 1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methyl-1,4-azaphosphinane 4-oxide (176 mg, 0.485 mmol), ethanol (5 mL), and 10% Pd/C (50 mg). The vessel was connected to a Parr apparatus, evacuated, and refilled with nitrogen. The vessel was then evacuated and filled with hydrogen gas to a pressure of 50 psi. The reaction mixture was shaken under 50 psi for 4 h. The mixture was filtered through Celite to a flask containing HCl in ethanol. Concentration of the filtrate afforded the compound as a gray solid (178 mg, 98% yield).

Example 57

5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidine-2,4-diamine

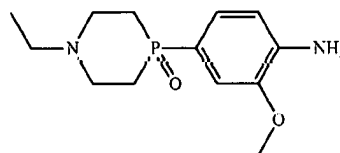


This compound can be prepared as in Example 32 by reacting 4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline with 2,4,5-trichloropyrimidine to generate 2,5-dichloro-N-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidin-4-amine. 2,5-dichloro-N-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidin-4-amine is then reacted with

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5-cyclopropyl-1,3-oxazol-2-amine according to the procedure described in Example 32.

4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline



Diethyl (3-methoxy-4-nitrophenyl)phosphonate

To a solution of 5-chloro-2-nitroanisole (1.00 g, 5.33 mmol) in 20 mL DMF was added diethyl phosphite (0.809 g, 5.86 mmol), palladium acetate (0.060 g, 0.27 mmol), XantPHOS (0.185 g, 0.320 mmol), and potassium phosphate (1.24 g, 5.86 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-45% ethyl acetate:heptane) to afford the desired product (0.504 g, 33% yield).

(3-methoxy-4-nitrophenyl)phosphonic dichloride

To a solution of diethyl (3-methoxy-4-nitrophenyl)phosphonate (4.54 g, 15.7 mmol) in 1.2 mL DMF was added thionyl chloride (5.7 mL, 78.5 mmol). The reaction flask was equipped with a reflux condenser and the mixture was heated to reflux. After 2 h at reflux, the reaction was cooled to rt and concentrated in vacuo. The crude oil was redissolved in CH_2Cl_2 and heptane was added to precipitate the desired compound. The clear solution was decanted and the precipitate was collected and dried to afford the desired compound as a white solid (1.39 g, 33% yield).

Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide

To a solution of (3-methoxy-4-nitrophenyl)phosphonic dichloride (1.39 g, 5.15 mmol) in 15 mL THF at -78° C. under nitrogen was slowly added vinylmagnesium bromide (10.3 mL, 1.0 M in THF). After the addition was complete, the reaction stirred at -78° C. for an additional hour. The cold reaction mixture was quenched by the addition of saturated NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 . The combined organic layers were washed with 1 M NaOH, brine, and dried over MgSO_4 . The organic extracts were filtered and concentrated to provide Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.982 g, 75%).

1-ethyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide

Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.480 g, 1.94 mmol), ethylamine hydrochloride (0.174 g, 2.12 mmol), and 1 N NaOH (2 mL) were dissolved in 50% aqueous THF (5 mL) and heated to 105° C. under nitrogen. After one hour, another portion of benzylamine was added to the reaction mixture. The reaction mixture was refluxed for an additional 2 h, and then cooled to rt. The reaction mixture was partitioned between saturated aqueous NaHCO_3 and CH_2Cl_2 .

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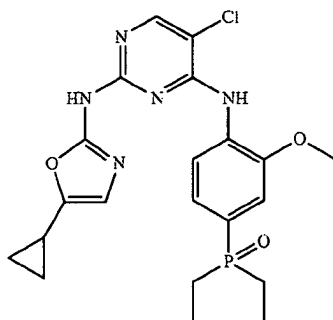
The aqueous phase was washed once with CH_2Cl_2 and the organic layers were combined. The organic extracts were washed with brine, dried over MgSO_4 , filtered, and concentrated. The residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the compound (0.267 g, 46% yield).

4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline

To a solution of 1-ethyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinan-4-oxide (0.267 g, 0.895 mmol) in 5 mL ethanol was added 10% Pd/C (27 mg) and 2.5 M HCl in ethanol (1.43 mL). The flask was equipped with a septum, evacuated, and refilled with hydrogen. The flask was equipped with a hydrogen balloon and the reaction stirred for 3 h. The flask was then evacuated and refilled with nitrogen. The reaction mixture was filtered through Celite and concentrated to provide the crude compound as the hydrochloride salt, which was used without purification.

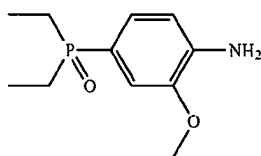
Example 58

5-chloro-N²-(2-cyclopropyl-1,3-oxazol-5-yl)-N⁴-[4-(diethylphosphoryl)-2-methoxyphenyl]pyrimidine-2,4-diamine



This compound can be prepared as in Example 32 by reacting 4-(diethylphosphoryl)-2-methoxyaniline with 2,4,5-trichloropyrimidine to 2,5-dichloro-N-[4-(diethylphosphoryl)-2-methoxyphenyl]pyrimidin-4-amine. 2,5-dichloro-N-[4-(diethylphosphoryl)-2-methoxyphenyl]pyrimidin-4-amine is then reacted with 5-cyclopropyl-1,3-oxazol-2-amine according to the procedure described in Example 32.

4-(Dipropylphosphoryl)-2-methoxyaniline



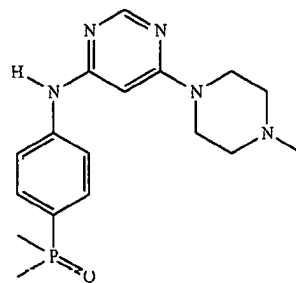
To a solution of 4-bromo-2-methoxyaniline (0.100 g, 0.495 mmol) in 2 mL DMF was added dipropylphosphine oxide (0.0730 g, 0.544 mmol), palladium acetate (5.6 mg, 0.025 mmol), XANTPHOS (17.2 mg, 0.030 mmol), and potassium phosphate (0.116 g, 0.544 mmol). The mixture was purged

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with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-12% 7N ammonia in methanol:dichloromethane) and the fractions were concentrated. The residue was acidified with 2.5 M HCl in ethanol and the solution was concentrated to provide 4-(dipropylphosphoryl)-2-methoxyaniline as the hydrochloride salt (0.132 g, 91% yield).

Example 59

N-[4-(dimethylphosphoryl)phenyl]-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine



6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine

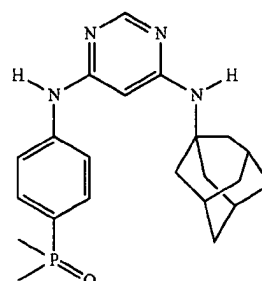
A suspension of 4-amino-dimethylphenylphosphine oxide (2.2 mmol) in 15 mL of N,N-Dimethylformamide and 3.6 mL of Diisopropylethylamine, is stirred at room temperature until a clear solution is obtained. 4,6-Dichloropyrimidine (2.6 mmol) is added in four portions over 5 minutes. The reaction mixture is stirred at high temperature until formation of the desired compound.

N-[4-(dimethylphosphoryl)phenyl]-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine

To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (0.072 mmol) in 1.5 mL of ethanol is added 10 μL of triethylamine and 1-Methyl piperazine (0.072 mmol). The mixture can be microwaved at 120 degrees. The reaction mixture can then be filtered through a syringe filter and can be purified by prep-HPLC.

Example 60

N-[4-(dimethylphosphoryl)phenyl]-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)pyrimidine-4,6-diamine

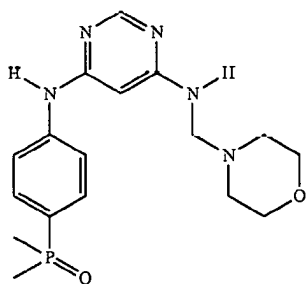


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To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.078 mmol) in 1.5 mL of ethanol is added 10 μ L of triethylamine and 1-Adamantanamine (12 mg, 0.078 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture can then be filtered through a syringe filter and purified by prep-HPLC.

Example 61

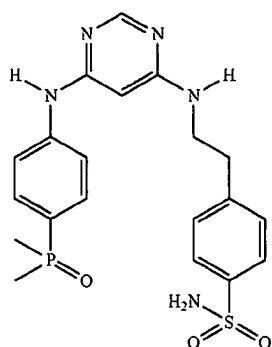
N-[4-(dimethylphosphoryl)phenyl]-N'-(morpholin-4-ylmethyl)pyrimidine-4,6-diamine



To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 4-(2-aminoethyl)morpholine (15 mg, 0.12 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture can be filtered through a syringe filter and purified by prep-HPLC.

Example 62

4-{2-[(6-{[4-(dimethylphosphoryl)phenyl]amino}pyrimidin-4-yl)-amino]ethyl}benzene sulfonamide

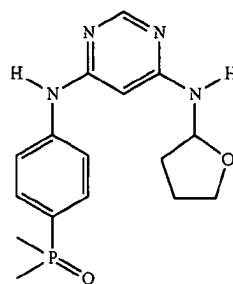


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To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 4-(2-aminoethyl)benzene-sulfonamide (23 mg, 0.12 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture can be filtered through a syringe filter and purified by prep-HPLC.

Example 63

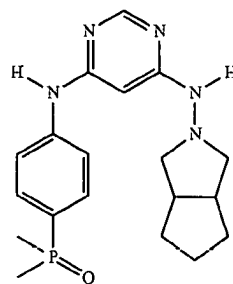
N-[4-(dimethylphosphoryl)phenyl]-N'-(tetrahydrofuran-2-yl)pyrimidine-4,6-diamine



To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and (s)-3-aminotetrahydrofuran hydrochloride salt (14 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture can then be filtered through a syringe filter and purified by prep-HPLC.

Example 64

N-[4-(dimethylphosphoryl)phenyl]-N'-(hexahydro-cyclopenta[c]pyrrol-2(1H)-yl)pyrimidine-4,6-diamine



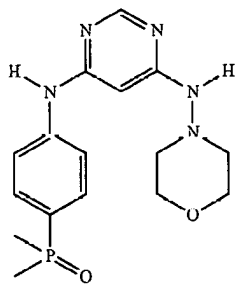
To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 3-Amino-3-azabicyclo-[3,3,0]octane hydrochloride salt (19 mg, 0.12 mmol). The mixture is microwaved at 120 degrees

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until formation of the desired compound. The reaction mixture can then be filtered through a syringe filter and purified by prep-HPLC.

Example 65

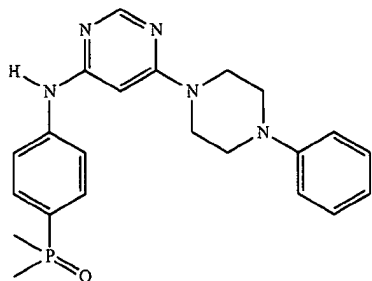
N-[4-(dimethylphosphoryl)phenyl]-N'-(morpholin-4-yl)pyrimidine-4,6-diamine



To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 4-Aminomorpholine (12 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture can then be filtered through a syringe filter and purified by prep-HPLC.

Example 66

N-[4-(dimethylphosphoryl)phenyl]-6-(4-phenylpiperazin-1-yl)pyrimidin-4-amine

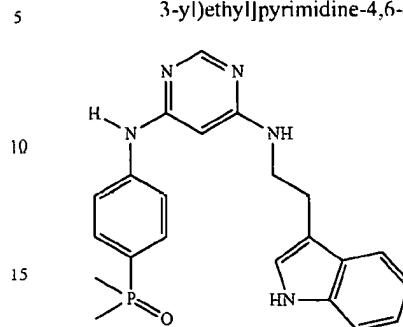


To a solution of 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine (prepared as in Example 59: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 1-Phenylpiperazine (19 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture can then be filtered through a syringe filter and purified by prep-HPLC.

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Example 67

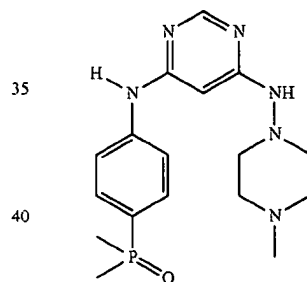
N-[4-(dimethylphosphoryl)phenyl]-N'-[2-(1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine



The compound is prepared as in Example 59 by reacting 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine with Tryptamine.

Example 68

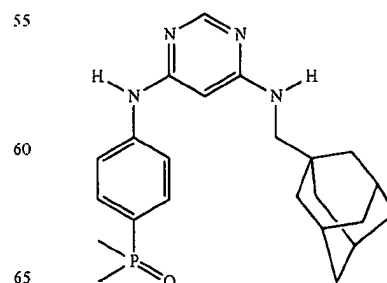
N-[4-(dimethylphosphoryl)phenyl]-N'-(4-methylpiperazin-1-yl)pyrimidine-4,6-diamine



The compound is prepared as in Example 59 by reacting 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine with 1-Amino-4-methylpiperazine.

Example 69

N-[4-(dimethylphosphoryl)phenyl]-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)pyrimidine-4,6-diamine

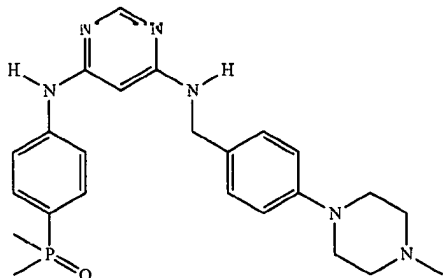


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The compound is prepared as in Example 59 by reacting 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine with 1-adamantanemethylamine.

Example 70

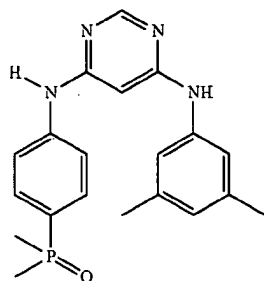
N-[4-(dimethylphosphoryl)phenyl]-N' [4-(4-methylpiperazin-1-yl)benzyl]pyrimidine-4,6-diamine



The compound is prepared as in Example 59 by reacting 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine with 4-(4-methylpiperazine)-benzylamine.

Example 71

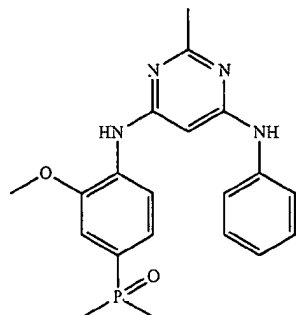
N-(3,5-dimethylphenyl)-N'-[4-(dimethylphosphoryl)phenyl]pyrimidine-4,6-diamine



The compound is prepared as in Example 59 by reacting 6-chloro-N-[4-(dimethylphosphoryl)phenyl]pyrimidin-4-amine with 3,5-dimethylaniline.

Example 72

N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-2-methyl-N'-phenylpyrimidine-4,6-diamine



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6-chloro-2-methyl-N-phenylpyrimidin-4-amine

To a solution of Aniline (205 mg, 2.2 mmol) and 4,6-dichloro-2-methylpyrimidine (2.7 mmol) in 5 mL of Ethanol, is added 500 mg of Potassium carbonate. The reaction mixture is stirred at room temperature until formation of the desired compound. Solvent is removed under reduced pressure. The residue can be purified by silica gel flash chromatography.

(3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide

To a solution of 5-Chloro-2-nitroanisole (0.5 g, 2.67 mmol) in 5 mL of DMF was added dimethylphosphine oxide (0.229 g, 2.93 mmol), palladium acetate (30 mg, 0.13 mmol), XANTHOS (0.092 g, 0.16 mmol) and potassium phosphate (0.623 g, 2.93 mmol). The mixture was purged with argon, and heated at 120° C. for 18 h. The reaction mixture was basified with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was concentrated and purified by prep-HPLC to give the final product (0.16 g, 30% yield). MS/ES+: m/z=229.

4-(dimethylphosphoryl)-2-methoxyaniline

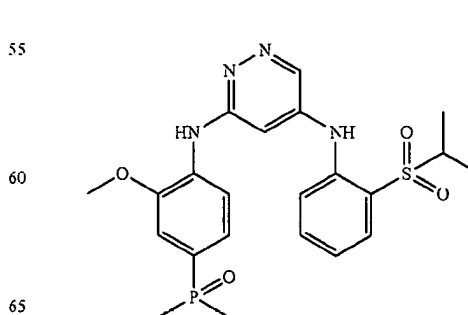
To a solution of (3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide (0.1 g, 0.44 mmol) in 5 mL of EtOH was added 10% weight of palladium on carbon (0.2 g). The mixture was purged with argon, and hydrogenated under 30 psi for 2 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.088 g, 86% yield). MS/ES+: m/z=199.

N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-2-methyl-N'-phenylpyrimidine-4,6-diamine

To a solution of 6-chloro-2-methyl-N-phenylpyrimidin-4-amine (0.35 mmol) and 4-(dimethylphosphoryl)-2-methoxyaniline (60 mg, 0.30 mmol) in 1 mL of DMF, is added 0.36 mL of 2.5M HCl in Ethanol. The reaction mixture can be heated in a sealed tube at 140 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

Example 73

N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine



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6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridazin-4-amine

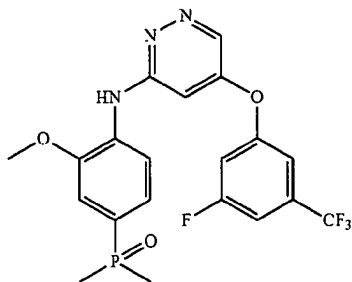
To a solution of 1-Amino-2-(isopropylsulphonyl)benzene (350 mg, 1.6 mmol) in 4 mL of N,N-Dimethyl formamide at 0 degree, is added Sodium hydride (100 mg) and the reaction mixture is allowed to stirred at 0 degree for 20 minutes. 3,5-dichloropyridazine (1.6 mmol) is added and the reaction mixture is warmed to room temperature. The reaction mixture is stirred at room temperature until formation of the desired compound. The reaction mixture is quenched with water and extracted with Ethyl acetate. The combined Ethyl acetate layers are dried over Sodium Sulfate and solvent is removed under reduced pressure. The residue can be purified by Prep-HPLC.

N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine

To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridazin-4-amine (0.02 mmol) and 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 72: 15 mg, 0.7 mmol) in 1 mL of 2-Methoxy ethanol, is added 1 mL of 2.5M HCl in Ethanol. The reaction mixture is heated in a sealed tube at 140 degree until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

Example 74

N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-[3-fluoro-5-(trifluoromethyl)phenoxy]pyridazin-3-amine



3-chloro-5-[3-fluoro-5-(trifluoromethyl)phenoxy]pyridazine

To a solution of 3-fluoro-5-(trifluoromethyl)phenol (1.6 mmol) in 4 mL of N,N-Dimethyl formamide at 0 degree, is added Sodium hydride (100 mg) and the reaction mixture is allowed to stirred at 0 degree for 20 minutes. 3,5-dichloropyridazine (1.6 mmol) is added and the reaction mixture is warmed to room temperature. The reaction mixture is stirred at room temperature until formation of the desired compound. The reaction mixture is quenched with water and extracted with Ethyl acetate. The combined Ethyl acetate layers are dried over Sodium Sulfate and solvent is removed under reduced pressure. The residue can be purified by Prep-HPLC.

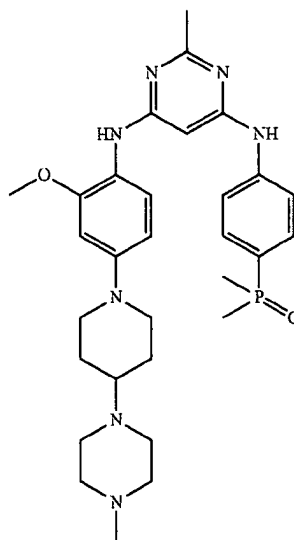
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N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-[3-fluoro-5-(trifluoromethyl)phenoxy]pyridazin-3-amine

To a solution of 3-chloro-5-[3-fluoro-5-(trifluoromethyl)phenoxy]pyridazine (0.02 mmol) and 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 72: 15 mg, 0.7 mmol) in 1 mL of 2-Methoxy ethanol, is added 1 mL of 2.5M HCl in Ethanol. The reaction mixture is heated in a sealed tube at 140 degree until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

Example 75

N-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]-2-methyl-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine



6-chloro-N-[4-(dimethylphosphoryl)phenyl]-2-methylpyrimidin-4-amine

To a solution of 4,6-dichloro-2-methylpyrimidine (1.31 mmol) in 1 mL of DMF is added 4-(dimethylphosphoryl)aniline (0.221 g, 1.31 mmol) and potassium carbonate (0.217 g, 1.57 mmol). The mixture is heated at 110° C. until formation of the desired compound. The reaction mixture is basified with saturated sodium bicarbonate solution. The suspension is filtered and washed with ethyl acetate.

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine

To a solution of 5-fluoro-2-nitroanisole (0.5 g, 2.92 mmol) in 3 mL of DMF was added 1-methyl-4-(piperidin)piperazine (0.536 g, 2.92 mmol) and potassium carbonate (0.808, 5.84 mmol). The mixture was heated at 120° C. for 18 h. The mixture was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was purified by chromatography to give final product as yellow solid (0.95 g, 95% yield). MS/ES+: m/z-334.

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2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline

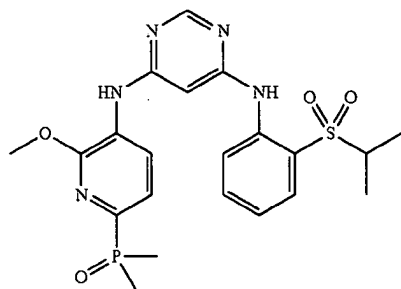
The a solution of 1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine (0.3 g, 0.90 mmol) in 10 mL of ethanol purged with argon was added 10% Palladium on carbon (0.060 g). The hydrogenation was finished under 30 psi after 4 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.15 g, 88% yield). MS/ES+: m/z=334.

N-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}-2-methyl-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine

To the compound 6-chloro-2-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (0.16 mmol) in 1 mL of 2-methoxyethanol is added 2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline (0.71 g, 0.16 mmol). The mixture is stirred at 110° C. until formation of the desired compound. The mixture is basified with saturated sodium bicarbonate solution and extracted with limited amount of ethyl acetate. The compound can be purified by chromatography.

Example 76

N-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine



6-(Dimethylphosphoryl)-2-methoxypyridin-3-ylamine

To a solution of 6-bromo-2-methoxypyridin-3-ylamine (0.203 g, 1.00 mmol) in 4 mL DMF was added dimethylphosphine oxide (0.171 g, 1.10 mmol), palladium acetate (11.0 mg, 0.0490 mmol), XANTPHOS (35.0 mg, 0.0600 mmol), and potassium phosphate (0.233 g, 1.10 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (77.2 mg, 39% yield).

6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine

To a solution of 1-Amino-2-(isopropylsulfonyl)benzene (0.955 g, 4.80 mmol) in 2 mL of DMF at 0° C. is added NaI (60% in oil, 0.349 g, 8.72 mmol) in one portion. After stirring for 20 min, 4,6-dichloropyrimidine can be added. The mix-

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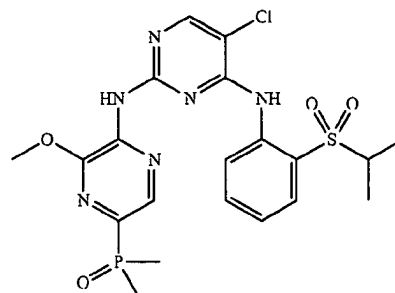
ture is stirred at 0° C. for 30 minutes, and then at room temperature until formation of the desired compound. After quenching with saturated ammonium chloride solution, the mixture is poured in water and ethyl acetate mixture. The compound can be purified by HPLC.

N-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine

To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (0.250 mmol) in 1 mL of 2-methoxyethanol is added 6-(dimethylphosphoryl)-2-methoxypyridin-3-ylamine (50.0 mg, 0.250 mmol) and 0.15 mL of 2.5 M HCl in ethanol. The mixture is heated in a sealed tube at 90° C. until formation of the desired compound. The mixture is basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers can be combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue can be purified by silica gel chromatography.

Example 77

N-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N'-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine



5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine

To a solution of 5-bromo-3-methoxypyrazin-3-ylamine (0.204 g, 1.00 mmol) in 4 mL DMF was added dimethylphosphine oxide (0.171 g, 1.10 mmol), palladium acetate (11.0 mg, 0.0490 mmol), XANTPHOS (35.0 mg, 0.0600 mmol), and potassium phosphate (0.233 g, 1.10 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (126 mg, 63% yield).

5-chloro-N²-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

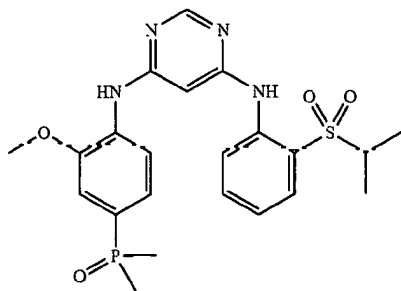
To a mixture of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (prepared in Example 76: 0.348 mmol) and 5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine (70.0 mg, 0.348 mmol) is added tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (17.6 mg, 0.017 mmol), XANTPHOS (23.3 mg, 0.040 mmol), and cesium

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carbonate (0.228 g, 0.700 mmol), and dioxane (3.5 mL). The tube is sealed and heated at 120° C. until formation of the desired compound. The reaction mixture is then cooled to room temperature and concentrated. The crude residue can be purified by silica gel chromatography.

Example 77

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine

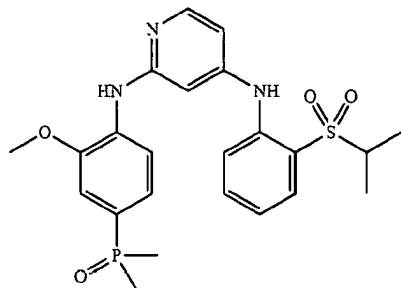


N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (prepared in Example 76: 0.054 mmol) in 0.5 mL of 2-methoxyethanol in a vial is added 4-(dimethylphosphoryl)-2-methoxyaniline (prepared in Example 73: 0.044 mmol) as the HCl salt. The vial is sealed and the reaction is heated at 90° C. until formation of the desired compound. The reaction is quenched with 1N NaOH solution and the solution extracted ethyl acetate. The organic layers are combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue can be purified by silica gel chromatography.

Example 79

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyridine-2,4-diamine



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2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridin-4-amine

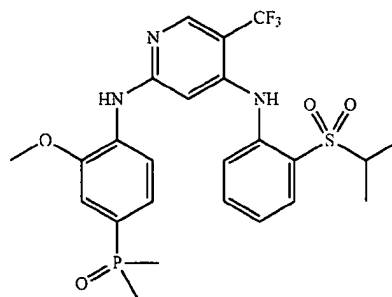
To a solution of 2-chloro-4-iodo-5-methylpyridine (2.00 mmol) in 8 mL toluene is added 1-amino-2-(isopropylsulfonyl)benzene (2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and cesium carbonate (2.20 mmol). The mixture is purged with nitrogen, and can be subjected to microwaves at 100° C. until formation of 2-chloro-5-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]pyridin-4-amine. The reaction mixture can then be concentrated and purified by silica gel chromatography.

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyridine-2,4-diamine

To a solution of 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridin-4-amine (0.12 mmol) in 1 mL of 2-methoxyethanol is added 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 72: 0.12 mmol) and 49 μL of 2.5 M HCl in ethanol. The mixture is heated in a sealed tube at 90° C. until formation of the desired compound. The mixture is then basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers can be combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue can be purified by prep-HPLC to afford the final compound.

Example 80

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridin-4-amine

To a solution of 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (2.00 mmol) in 8 mL toluene is added 1-amino-2-(isopropylsulfonyl)benzene (2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and cesium carbonate (2.20 mmol). The mixture is purged with nitrogen, and can be subjected to microwaves at 100° C. until formation of 2-chloro-5-methyl-N-[2-(propan-2-ylsulfonyl)phenyl]pyridin-4-amine. The reaction mixture can then be concentrated and purified by silica gel chromatography.

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyridine-2,4-diamine

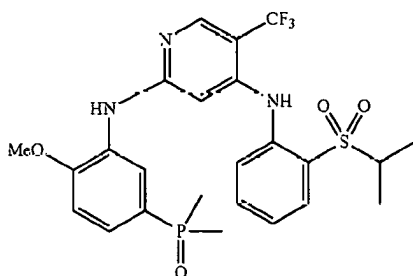
To a solution of 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridin-4-amine (0.12 mmol) in 1

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mL of 2-methoxyethanol is added 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 72: 0.12 mmol) and 49 μ L of 2.5 M HCl in ethanol. The mixture is heated in a sealed tube at 90° C. until formation of the desired compound. The mixture is then basified with 1N NaOH solution, and extracted with ethyl acetate. The organic layers can be combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue can be purified by prep-HPLC to afford the final compound.

Example 81

N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



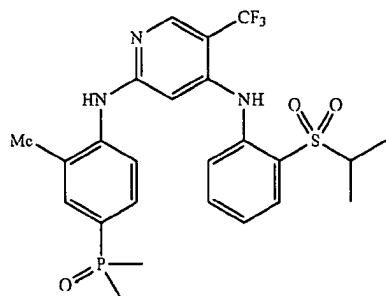
This compound can be prepared as described in Example 80 by reacting 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-4-amine with 5-(Dimethylphosphoryl)-2-methoxyaniline.

5-(Dimethylphosphoryl)-2-methoxyaniline

To a solution of 5-bromo-2-methoxyaniline (0.404 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.365 g, 85% yield).

Example 82

N²-[4-dimethylphosphoryl]-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



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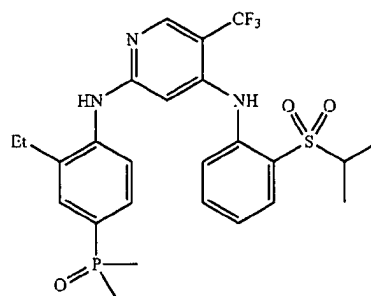
This compound can be prepared as described in Example 80 by reacting 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-4-amine with 4-(Dimethylphosphoryl)-2-methylaniline.

4-(Dimethylphosphoryl)-2-methylaniline

To a solution of 4-bromo-2-methylaniline (0.372 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.313 g, 85% yield).

Example 83

N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



This compound can be prepared as described in Example 80 by reacting 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-4-amine with 4-(Dimethylphosphoryl)-2-ethylaniline.

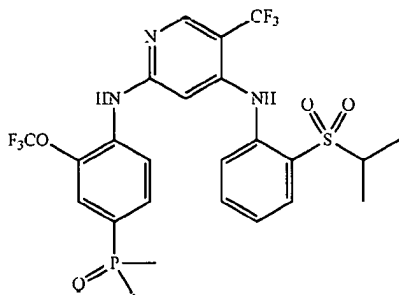
4-(Dimethylphosphoryl)-2-ethylaniline

To a solution of 4-bromo-2-ethylaniline (0.400 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.308 g, 78% yield).

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Example 84

N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



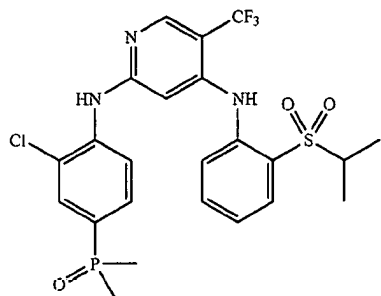
This compound can be prepared as described in Example 80 by reacting 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-4-amine with 4-(Dimethylphosphoryl)-2-(trifluoromethoxy)aniline.

4-(Dimethylphosphoryl)-2-(trifluoromethoxy)aniline

To a solution of 4-iodo-2-(trifluoromethoxy)aniline (0.606 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) and acidified with HCl in methanol to afford the desired product as its hydrochloride salt (0.573 g, 98% yield).

Example 85

N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



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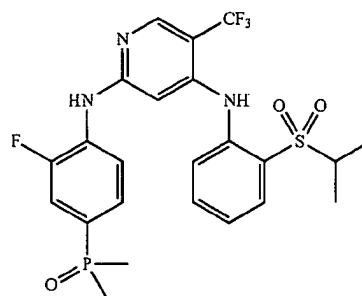
This compound can be prepared as described in Example 80 by reacting 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-4-amine with 2-chloro-4-(dimethylphosphoryl)aniline.

2-Chloro-4-(dimethylphosphoryl)aniline

To a solution of 2-chloro-4-iodoaniline (0.507 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.340 g, 83% yield).

Example 86

N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine



This compound can be prepared as described in Example 80 by reacting 2-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-4-amine with 4-(dimethylphosphoryl)-2-fluoroaniline.

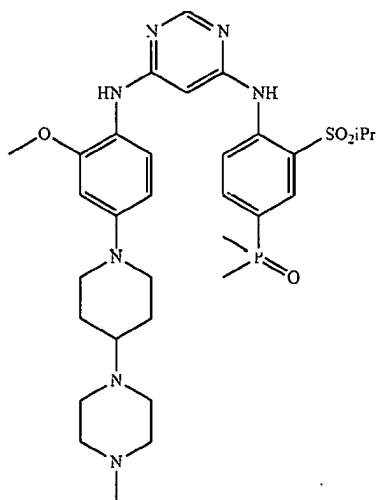
4-(Dimethylphosphoryl)-2-fluoroaniline

To a solution of 4-bromo-2-fluoroaniline (0.380 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (73.5 mg, 20% yield).

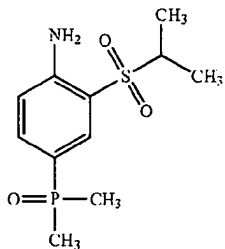
223

Example 87

N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-4,6-diamine



4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline



4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene

At 0 degree, to a stirring solution of 4-Bromo-2-Fluorobenzene (2.0 g, 9.1 mmol) in DCM was added Sodium 2-propane thiolate (2.0 g, 20 mmol) in two portions. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through a syringe filter. The product was isolated by prep-HPLC (water/Acetonitrile) as a bright yellow solid (0.8 g, 2.9 mmol, 32% yield).

4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene

To a stirring solution of 4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene (0.8 g, 2.9 mmol) in Acetic Acid (10 ml)

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was added Hydrogen Peroxide (30% aqueous solution, 0.6 mL, 5.8 mmol). The reaction mixture was heated to 110 degrees C. for 2 hours in oil bath. The reaction mixture was treated with saturated Sodium Sulfide aqueous solution and basified with saturated sodium bicarbonate solution. The mixture was extracted with Ethyl Acetate and the combined organic layers were dried over sodium sulfate. The organic solvent was removed under reduced pressure and the residue was used for the next step reaction without further purification.

Dimethyl[4-nitro-3-(propan-2-ylsulfonyl)phenyl]phosphane oxide

To a stirring solution of 4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene (0.44 g, 1.6 mmol) and Dimethyl Phosphine oxide (0.15 g, 1.9 mmol) in 1 mL of DMF, was added Potassium Phosphate (0.37 g, 1.8 mmol), Pd(OAc)₂ (18 mg, 0.08 mmol), Xanphos (55 mg, 0.10 mmol). The reaction mixture was stirred at 110 degrees C. overnight. The reaction mixture was cooled to room temperature and filtered through celite. The desired product was isolated through prep-HPLC to yield a brownish yellow solid (0.24 g, 55% yield).

4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline

To a solution of dimethyl[4-nitro-3-(propan-2-ylsulfonyl)phenyl]phosphane oxide (0.24 g, 0.88 mmol) in Ethanol was added Pd on carbon (10% w/w, 24 mg) and stirred under hydrogen overnight. The reaction mixture was filtered and the organic solvent was removed under reduced pressure. The residue was purified by prep-HPLC to yield 100 mg of desired product (50% yield).

6-chloro-N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine

To a solution of 4,6-dichloropyrimidine (1.31 mmol) in 1 mL of DMF is added 4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline (1.31 mmol) and potassium carbonate (0.217 g, 1.57 mmol). The mixture is heated at 110° C. until formation of the desired compound. The reaction mixture is basified with saturated sodium bicarbonate solution. The suspension is filtered and washed with ethyl acetate.

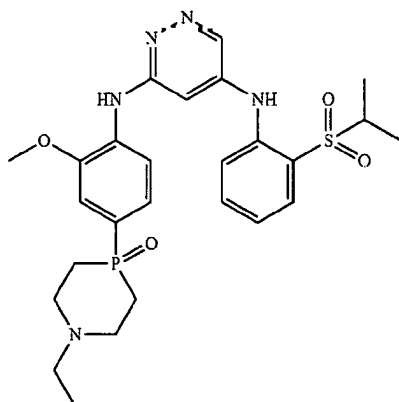
N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-4,6-diamine

To the compound 6-chloro-N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]pyrimidin-4-amine (0.16 mmol) in 1 mL of 2-methoxyethanol is added 2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline (prepared in Example 75: 0.71 g, 0.16 mmol). The mixture is stirred at 110° C. until formation of the desired compound. The mixture is basified with saturated sodium bicarbonate solution and extracted with limited amount of ethyl acetate. The compound can be purified by chromatography.

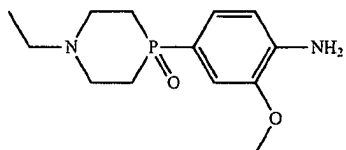
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Example 88

N^3 -[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl] N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine



4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline



Diethyl (3-methoxy-4-nitrophenyl)phosphonate

To a solution of 5-chloro-2-nitroanisole (1.00 g, 5.33 mmol) in 20 mL DMF was added diethyl phosphite (0.809 g, 5.86 mmol), palladium acetate (0.060 g, 0.27 mmol), XANTPHOS (0.185 g, 0.320 mmol), and potassium phosphate (1.24 g, 5.86 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-45% ethyl acetate:heptane) to afford the desired product (0.504 g, 33% yield).

(3-methoxy-4-nitrophenyl)phosphonic dichloride

To a solution of diethyl (3-methoxy-4-nitrophenyl)phosphonate (4.54 g, 15.7 mmol) in 1.2 mL DMF was added thionyl chloride (5.7 mL, 78.5 mmol). The reaction flask was equipped with a reflux condenser and the mixture was heated to reflux. After 2 h at reflux, the reaction was cooled to rt and concentrated in vacuo. The crude oil was redissolved in CH_2Cl_2 and heptane was added to precipitate the desired compound. The clear solution was decanted and the precipitate was collected and dried to afford the desired compound as a white solid (1.39 g, 33% yield).

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Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide

To a solution of (3-methoxy-4-nitrophenyl)phosphonic dichloride (1.39 g, 5.15 mmol) in 15 mL THF at -78° C. under nitrogen was slowly added vinylmagnesium bromide (10.3 mL, 1.0 M in THF). After the addition was complete, the reaction stirred at -78° C. for an additional hour. The cold reaction mixture was quenched by the addition of saturated NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 . The combined organic layers were washed with 1 M NaOH, brine, and dried over $MgSO_4$. The organic extracts were filtered and concentrated to provide Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.982 g, 75%).

1-ethyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide

Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.480 g, 1.94 mmol), ethylamine hydrochloride (0.174 g, 2.12 mmol), and 1 N NaOH (2 mL) were dissolved in 50% aqueous THF (5 mL) and heated to 105° C. under nitrogen. After one hour, another portion of benzylamine was added to the reaction mixture. The reaction mixture was refluxed for an additional 2 h, and then cooled to rt. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2 . The aqueous phase was washed once with CH_2Cl_2 and the organic layers were combined. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the compound (0.267 g, 46% yield).

4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline

To a solution of 1-ethyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide (0.267 g, 0.895 mmol) in 5 mL ethanol was added 10% Pd/C (27 mg) and 2.5 M HCl in ethanol (1.43 mL). The flask was equipped with a septum, evacuated, and refilled with hydrogen. The flask was equipped with a hydrogen balloon and the reaction stirred for 3 h. The flask was then evacuated and refilled with nitrogen. The reaction mixture was filtered through Celite and concentrated to provide the crude compound as the hydrochloride salt, which was used without purification.

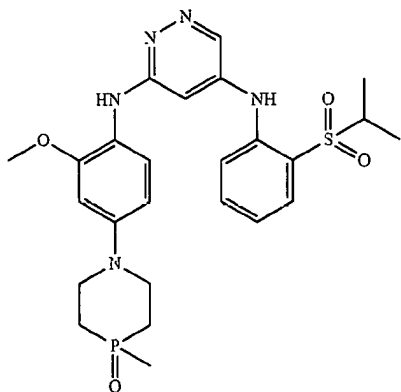
N^3 -[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl] N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine

To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-4-amine (prepared in Example 73: 0.02 mmol) and 4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline (0.7 mmol) in 1 mL of 2-Methoxy ethanol, is added 1 mL of 2.5M HCl in Ethanol. The reaction mixture is heated in a sealed tube at 140 degree until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

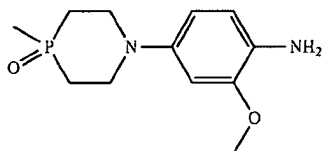
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Example 89

N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine



2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline



1-benzyl-4-methyl-1,4-azaphosphinane 4-oxide

To a solution of methylphosphonic dichloride (10.0 g, 75.2 mmol) in CH₂Cl₂ at -78° C., was added vinylmagnesium bromide (175 mL, 1.0 M in THF) via addition funnel over 4 h. The solution was warmed to 0° C. and quenched with a minimum amount of saturated NH₄Cl. The mixture was filtered through a pad of silica gel and silica was extracted with 10% 7N ammonia in methanol:dichloromethane. The solution was concentrated under reduced pressure to afford methyl divinyl phosphine oxide as a viscous, yellow oil that was used without purification.

A solution of methyl divinyl phosphine oxide (1.16 g, 10.0 mmol) and benzylamine (1.20 mL, 11.0 mmol) in 1:1 THF/water (25 mL) was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol: dichloromethane) to afford 1-benzyl-4-methyl-[1,4]azaphosphinane-4-oxide as a white solid (1.57 g, 70% yield).

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4-methyl-[1,4]azaphosphinane-4-oxide

A flask was charged with 1-benzyl-4-methyl-[1,4]azaphosphinane-4-oxide (1.00 g, 4.47 mmol) and 10% Pd/C (100 mg). The flask was evacuated and filled with nitrogen. Anhydrous methanol (18 mL) was added to the flask and the flask was equipped with a reflux condenser with a nitrogen inlet. Ammonium formate (2.25 g, 35.8 mmol) was added in one portion at room temperature. The resulting mixture was stirred at reflux for 2 h. The reaction was filtered through a Celite pad and the Celite was washed with 2x5 mL methanol. The combined filtrate and washing was evaporated in vacuo. The crude residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford 4-methyl-[1,4]azaphosphinane-4-oxide as a yellow gel (0.589 g, 99% yield).

1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide

A mixture of 4-methyl-[1,4]azaphosphinane-4-oxide (133 mg, 1.00 mmol), 5-fluoro-2-nitroanisole (340 mg, 2.00 mmol), K₂CO₃ (345 mg, 2.50 mmol), and DMF (5 mL) was heated to 50° C. After 2 h, the reaction mixture was concentrated and purified by silica gel chromatography (0-5% 7N ammonia in methanol:dichloromethane) to afford 1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide as a bright yellow solid (272 mg, 96% yield).

2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline

To a pressure vessel was added 1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide (272 mg, 0.960 mmol), ethanol (5 mL), and 10% Pd/C (50 mg). The vessel was connected to a Parr apparatus, evacuated, and refilled with hydrogen gas to a pressure of 50 psi. The reaction mixture was shaken under 50 psi for 4 h. The mixture was filtered through Celite to a flask containing HCl in ethanol. Concentration of the filtrate afforded 2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline as a gray solid (211 mg, 87% yield).

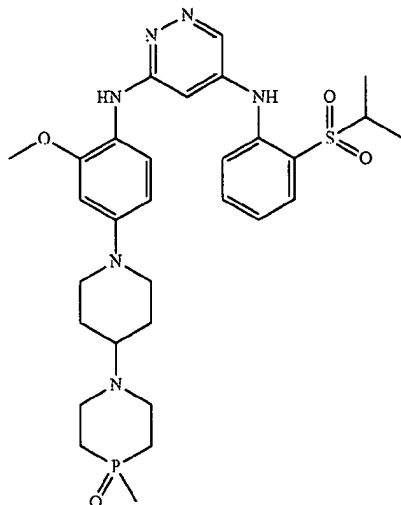
N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine

To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-4-amine (prepared in Example 73: 0.02 mmol) and 2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline (0.7 mmol) in 1 mL of 2-Methoxy ethanol, is added 1 mL of 2.5M HCl in Ethanol. The reaction mixture is heated in a sealed tube at 140 degree until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

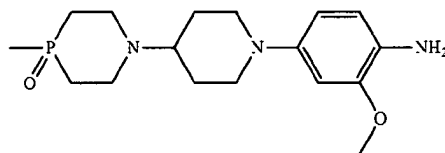
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Example 90

N^3 -[2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine



2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline



tert-butyl 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidine-1-carboxylate

A solution of methyl divinyl phosphine oxide (140 mg, 1.21 mmol) and 1-Boc-4-aminopiperidine (265 mg, 1.33 mmol) in 1:1 THF/water (3 mL) was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired compound as a white solid (178 mg, 38% yield).

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methyl-1,4-azaphosphinane 4-oxide

To a stirring solution of tert-butyl 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidine-1-carboxylate (178 mg, 0.563 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.5 mL). After 20 min, the solution was concentrated and the resulting residue was redissolved in DMF (2 mL). Potassium carbonate (160 mg, 1.16 mmol) was added portionwise to the stirring solution followed by 5-fluoro-2-nitroanisole (158

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mg, 0.930 mmol). The reaction mixture was heated to 50° C. After 2 h, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the compound as a bright yellow solid (176 mg, 86% yield).

2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline

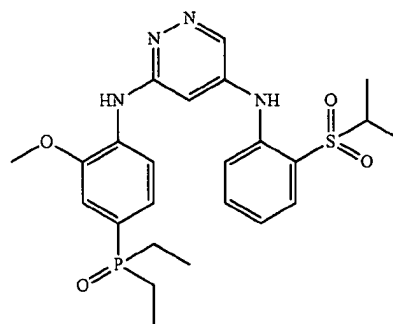
To a pressure vessel was added 1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methyl-1,4-azaphosphinane 4-oxide (176 mg, 0.485 mmol), ethanol (5 mL), and 10% Pd/C (50 mg). The vessel was connected to a Parr apparatus, evacuated, and refilled with nitrogen. The vessel was then evacuated and filled with hydrogen gas to a pressure of 50 psi. The reaction mixture was shaken under 50 psi for 4 h. The mixture was filtered through Celite to a flask containing HCl in ethanol. Concentration of the filtrate afforded the compound as a gray solid (178 mg, 98% yield).

N^3 -[2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine

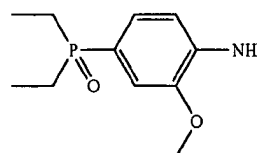
To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-4-amine (prepared in Example 73: 0.02 mmol) and 2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline (0.7 mmol) in 1 mL of 2-Methoxy ethanol, is added 1 mL of 2.5M HCl in Ethanol. The reaction mixture is heated in a sealed tube at 140 degree until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

Example 91

N^3 -[4-(diethylphosphoryl)-2-methoxyphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine



4-(Dipropylphosphoryl)-2-methoxyaniline



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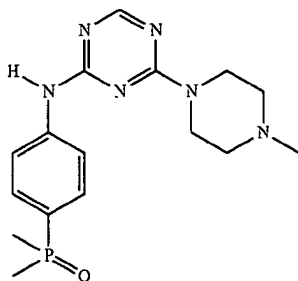
To a solution of 4-bromo-2-methoxyaniline (0.100 g, 0.495 mmol) in 2 mL DMF was added dipropylphosphine oxide (0.0730 g, 0.544 mmol), palladium acetate (5.6 mg, 0.025 mmol), XANTPHOS (17.2 mg, 0.030 mmol), and potassium phosphate (0.116 g, 0.544 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-12% 7N ammonia in methanol:dichloromethane) and the fractions were concentrated. The residue was acidified with 2.5 M HCl in ethanol and the solution was concentrated to provide 4-(dipropylphosphoryl)-2-methoxyaniline as the hydrochloride salt (0.132 g, 91% yield).

N³-[4-(diethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine

To a solution of 6-chloro-N-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-4-amine (prepared in Example 73: 0.02 mmol) and 4-(Dipropylphosphoryl)-2-methoxyaniline (0.7 mmol) in 1 mL of 2-Methoxy ethanol, is added 1 mL of 2.5M HCl in Ethanol. The reaction mixture is heated in a sealed tube at 140 degree until formation of the desired compound. The reaction mixture is filtered through a syringe filter and can be purified by Prep-HPLC.

Example 92

N-[4-(dimethylphosphoryl)phenyl]-4-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-amine



4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazine-2-amine

A suspension of 4-amino-dimethylphenylphosphine oxide (3.7 g, 2.2 mmol) in 15 mL of N,N-Dimethylacetamide and 3.6 mL of Diisopropylethylamine, can be stirred at room temperature for 15 minutes until a clear solution is obtained. 2,4-Dichloro-1,3,5-triazine (2.6 mmol) is added in four portions over 5 minutes. The reaction mixture is stirred at 60 degrees for 1 hour. The reaction mixture is cooled to room temperature, filtered and purified by prep-HPLC.

N-[4-(dimethylphosphoryl)phenyl]-4-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-amine

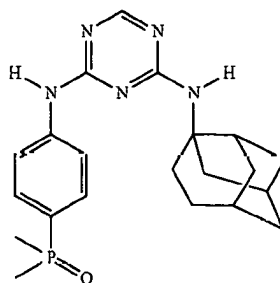
To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazine-2-amine (0.072 mmol) in 1.5 mL of ethanol is added 10 µL of triethylamine and 1-Methyl piperazine (7.2 mg, 0.072 mmol). The mixture can be microwaved at 120

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degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 93

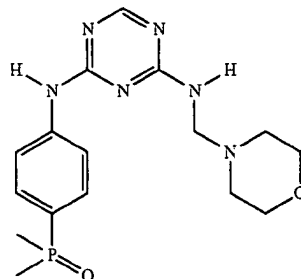
N-[4-(dimethylphosphoryl)phenyl]-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3,5-triazine-2,4-diamine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazine-2-amine (prepared as in Example 92: 0.078 mmol) in 1.5 mL of ethanol is added 10 µL of triethylamine and 1-Adamantanamine (12 mg, 0.078 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 94

N-[4-(dimethylphosphoryl)phenyl]-N'-(morpholin-4-ylmethyl)-1,3,5-triazine-2,4-diamine

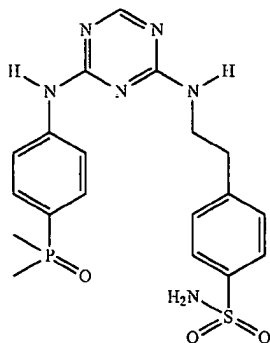


To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazine-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 µL of triethylamine and 4-(2-aminoethyl)morpholine (15 mg, 0.12 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

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Example 95

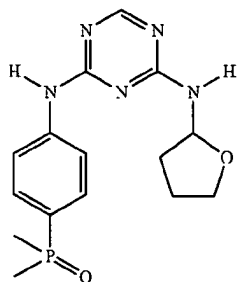
4-{2-[(4-{[4-(dimethylphosphoryl)phenyl]amino}-1,3,5-triazin-2-yl)amino]ethyl}benzene sulfonamide



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 4-(2-aminoethyl)benzene-sulfonamide (23 mg, 0.12 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 96

N-[4-(dimethylphosphoryl)phenyl]-N'-(tetrahydrofuran-2-yl)-1,3,5-triazine-2,4-diamine

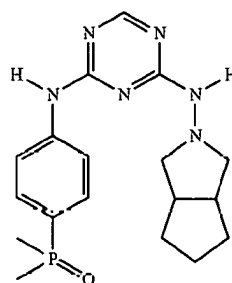


To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and (S)-3-aminotetrahydrofuran hydrochloride salt (14 mg, 0.12 mmol). The mixture can be microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

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Example 97

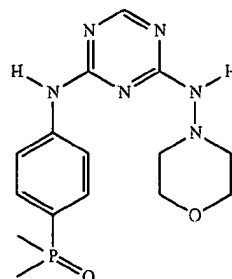
N-[4-(dimethylphosphoryl)phenyl]-N'-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-1,3,5-triazine-2,4-diamine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 3-Amino-3-azabicyclo-[3.3.0]octane hydrochloride salt (19 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 98

N-[4-(dimethylphosphoryl)phenyl]-N'-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine

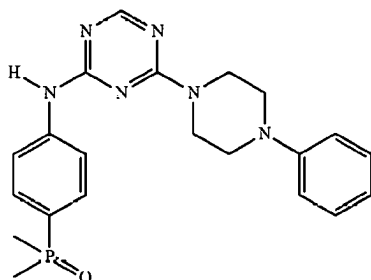


To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 4-Aminomorpholine (12 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

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Example 99

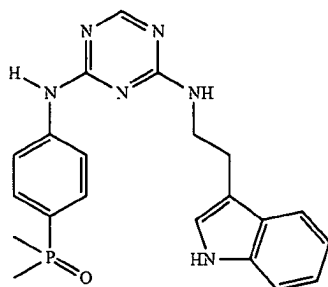
N-[4-(dimethylphosphoryl)phenyl]-4-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 1-Phenylpiperazine (19 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 100

N-[4-(dimethylphosphoryl)phenyl]-N-[2-(1H-indol-3-yl)ethyl]-1,3,5-triazine-2,4-diamine

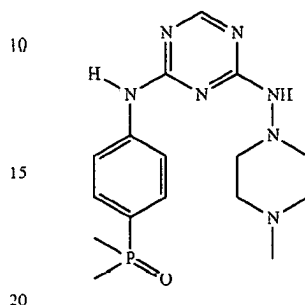


To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and Tryptamine (18 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

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Example 101

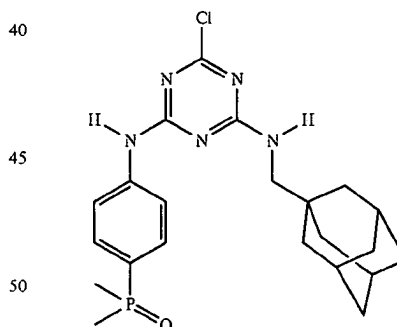
N-[4-(dimethylphosphoryl)phenyl]-N'-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine



To a solution of 4-chloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 92: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 1-Amino-4-methyl-piperazine (13 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 102

6-chloro-N-[4-(dimethylphosphoryl)phenyl]-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-1,3,5-triazine-2,4-diamine



4,6-dichloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine

A suspension of 4-amino-dimethylphenylphosphine oxide (3.7 g, 2.2 mmol) in 15 mL of N,N-Dimethylformamide and 3.6 mL of Diisopropylethylamine is cooled to 0° C. 2,4,6-trichloro-1,3,5-triazine (2.6 mmol) is added in four portions over 5 minutes. The reaction mixture is warmed up to room temperature and stirred until formation of the desired compound. The reaction mixture is filtered and purified by prep-HPLC.

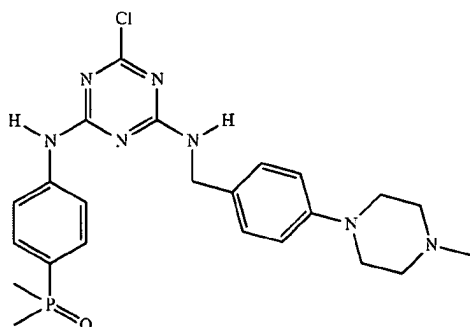
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6-chloro-N-[4-(dimethylphosphoryl)phenyl]-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-1,3,5-triazine-2,4-diamine

To a solution of 4,6-dichloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (0.072 mmol) in 1.5 mL of ethanol is added 10 μ L of triethylamine and 1-(1-adamantyl)-methanamine (7.2 mg, 0.072 mmol). The mixture can be microwaved at 120 degrees for 20 minutes. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 103

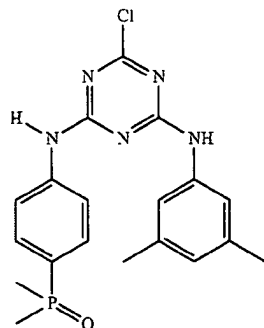
6-chloro-N-[4-(dimethylphosphoryl)phenyl]-N'-(4-(4-methylpiperazin-1-yl)benzyl)-1,3,5-triazine-2,4-diamine



To a solution of 4,6-dichloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 102: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine and 4-(4-methylpiperazine)-benzylamine (24 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 104

6-chloro-N-(3,5-dimethylphenyl)-N'-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazine-2,4-diamine



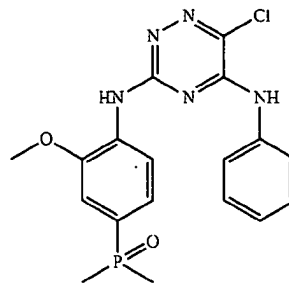
To a solution of 4,6-dichloro-N-[4-(dimethylphosphoryl)phenyl]-1,3,5-triazin-2-amine (prepared as in Example 102: 0.12 mmol) in 2 mL of ethanol is added 50 μ L of triethylamine

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and 3,5-dimethylaniline (24 mg, 0.12 mmol). The mixture is microwaved at 120 degrees until formation of the desired compound. The reaction mixture is filtered through a syringe filter and purified by prep-HPLC.

Example 105

6-chloro-N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-phenyl-1,2,4-triazine-3,5-diamine



3,6-dichloro-N-phenyl-1,2,4-triazin-5-amine

To a solution of Aniline (205 mg, 2.2 mmol) and 3,5,6-trichloro-1,2,4-triazine (2.7 mmol) in CH₂Cl₂, is added triethylamine (3 mmol). The reaction mixture is stirred at room temperature until formation of the desired product. Solvent is removed under reduced pressure. The residue can be purified by silica gel flash chromatography.

(3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide

To a solution of 5-Chloro-2-nitroanisole (0.5 g, 2.67 mmol) in 5 mL of DMF was added dimethylphosphine oxide (0.229 g, 2.93 mmol), palladium acetate (30 mg, 0.13 mmol), XANTPHOS (0.092 g, 0.16 mmol) and potassium phosphate (0.623 g, 2.93 mmol). The mixture was purged with argon, and heated at 120° C. for 18 h. The reaction mixture was basified with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was concentrated and purified by prep-HPLC to give the final product (0.16 g, 30% yield). MS/ES+: m/z=229.

4-(dimethylphosphoryl)-2-methoxyaniline

To a solution of (3-methoxy-4-nitrophenyl)(dimethyl)phosphane oxide (0.1 g, 0.44 mmol) in 5 mL of EtOH was added 10% weight of palladium on carbon (0.2 g). The mixture was purged with argon, and hydrogenated under 30 psi for 2 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.088 g, 86% yield). MS/ES+: m/z=199.

6-chloro-N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-phenyl-1,2,4-triazine-3,5-diamine

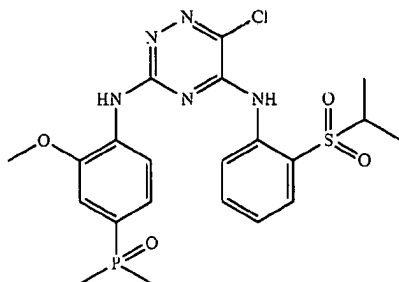
A mixture of 3,6-dichloro-N-phenyl-1,2,4-triazin-5-amine (1 mmol), 4-(dimethylphosphoryl)-2-methoxyaniline (1 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 h in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na₂CO₃. The dichloro-

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dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 106

6-chloro-N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine

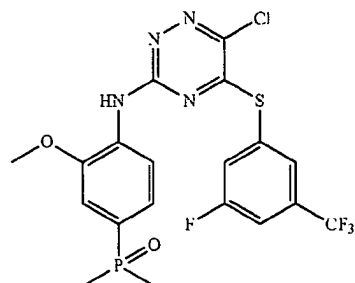
To a solution of 1-Amino-2-(isopropylsulphonyl)benzene (350 mg, 1.6 mmol) and 3,5,6-trichloro-1,2,4-triazine (1.6 mmol) in CH_2Cl_2 , is added triethylamine (2 mmol). The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

6-chloro-N⁴-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (1 mmol), 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 105: 1 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 107

6-chloro-N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-[[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl]-1,2,4-triazin-3-amine



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3,6-dichloro-5-[[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl]-1,2,4-triazine

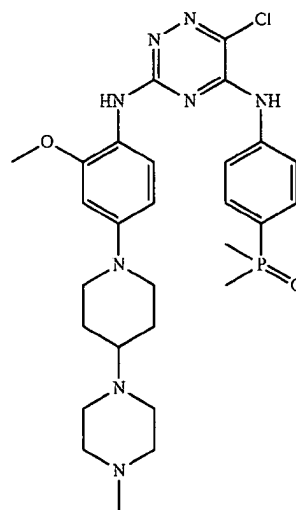
To a solution of 3,5,6-trichloro-1,2,4-triazine (3 mmol) in dry THF (30 mL) at -78°C . under nitrogen atmosphere is added 3-fluoro-5-(trifluoromethyl)benzenethiol (3 mmol) and sodium carbonate (3 mmol). The reaction is allowed to reach room temperature and is stirred at room temperature until formation of the desired compound. The solvent is evaporated. The residue is suspended in water and extracted with CH_2Cl_2 . The dichloromethane solution is dried over MgSO_4 and evaporated. The residue is chromatographed on a silica gel column.

6-chloro-N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-[[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl]-1,2,4-triazin-3-amine

A mixture of 3,6-dichloro-5-[[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl]-1,2,4-triazine (0.7 mmol), 4-(dimethylphosphoryl)-2-methoxyaniline (prepared as in Example 105: 15 mg, 0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 108

6-chloro-N⁵-[4-(dimethylphosphoryl)phenyl]-N³-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]-1,2,4-triazine-3,5-diamine



3,6-dichloro-N-[4-(dimethylphosphoryl)phenyl]-1,2,4-triazin-5-amine

To a solution of 4-amino-dimethylphenylphosphine oxide (1.6 mmol) and 3,5,6-trichloro-1,2,4-triazine (1.6 mmol) in CH_2Cl_2 , is added triethylamine (2 mmol). The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of

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Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine

To a solution of 5-fluoro-2-nitroanisole (0.5 g, 2.92 mmol) in 3 mL of DMF was added 1-methyl-4-(piperidin)piperazine (0.536 g, 2.92 mmol) and potassium carbonate (0.808, 5.84 mmol). The mixture was heated at 120° C. for 18 h. The mixture was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was purified by chromatography to give final product as yellow solid (0.95 g, 95% yield). MS/ES+: $m/z=334$.

2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline

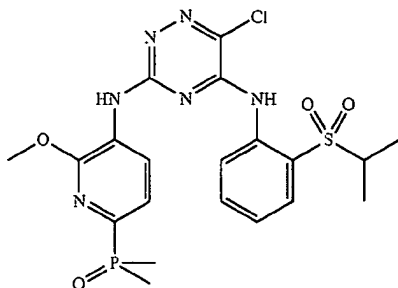
The a solution of 1-[1(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methylpiperazine (0.3 g, 0.90 mmol) in 10 mL of ethanol purged with argon was added 10% Palladium on carbon (0.060 g). The hydrogenation was finished under 30 psi after 4 h. The mixture was passed through Celite to a flask containing HCl in ethanol. Concentration of the filtrate gave the final product (0.15 g, 88% yield). MS/ES+: $m/z=334$.

6-chloro- N^3 -[4-(dimethylphosphoryl)phenyl]- N^3 -[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro-N-[4-(dimethylphosphoryl)phenyl]-1,2,4-triazin-5-amine (0.7 mmol), 2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 109

6-chloro- N^3 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



6-(Dimethylphosphoryl)-2-methoxypyridin-3-ylamine

To a solution of 6-bromo-2-methoxypyridin-3-ylamine (0.203 g, 1.00 mmol) in 4 mL DMF was added dimethylphosphine oxide (0.171 g, 1.10 mmol), palladium acetate (11.0

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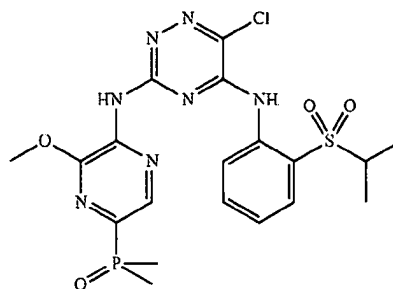
mg, 0.0490 mmol), XANTPHOS (35.0 mg, 0.0600 mmol), and potassium phosphate (0.233 g, 1.10 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (77.2 mg, 39% yield).

6-chloro- N^3 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106: 0.7 mmol), 6-(Dimethylphosphoryl)-2-methoxypyridin-3-ylamine (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 110

6-chloro- N^3 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine

To a solution of 5-bromo-3-methoxypyrazin-3-ylamine (0.204 g, 1.00 mmol) in 4 mL DMF was added dimethylphosphine oxide (0.171 g, 1.10 mmol), palladium acetate (11.0 mg, 0.0490 mmol), XANTPHOS (35.0 mg, 0.0600 mmol), and potassium phosphate (0.233 g, 1.10 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired product (126 mg, 63% yield).

6-chloro- N^3 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

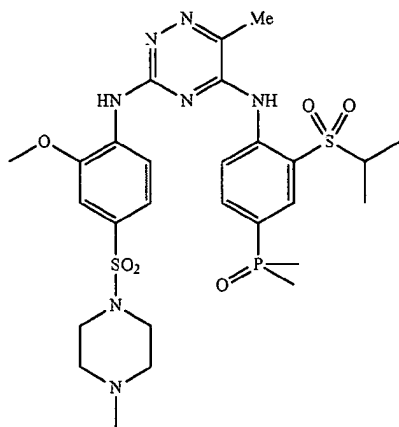
A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106: 0.7 mmol), 5-(dimethylphosphoryl)-3-methoxypyrazin-2-amine (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichlo-

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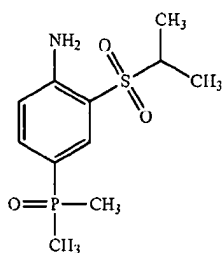
romethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 111

N^5 -[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]- N^3 -{2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine



4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline



4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene

At 0 degree, to a stirring solution of 4-Bromo-2-Fluorobenzene (2.0 g, 9.1 mmol) in DCM was added Sodium propane-2-thiolate (2.0 g, 20 mmol) in two portions. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through a syringe filter. The product was isolated by prep-HPLC (water/Acetonitrile) as a bright yellow solid (0.8 g, 2.9 mmol, 32% yield).

4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene

To a stirring solution of 4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene (0.8 g, 2.9 mmol) in Acetic Acid (10 mL) was added Hydrogen Peroxide (30% aqueous solution, 0.6 mL, 5.8 mmol). The reaction mixture was heated to 110 degrees C. for 2 hours in oil bath. The reaction mixture was

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treated with saturated Sodium Sulfide aqueous solution and basified with saturated sodium bicarbonate solution. The mixture was extracted with Ethyl Acetate and the combined organic layers were dried over sodium sulfate. The organic solvent was removed under reduced pressure and the residue was used for the next step reaction without further purification.

Dimethyl[4-nitro-3-(propan-2-ylsulfonyl)phenyl]phosphane oxide

To a stirring solution of 4-bromo-1-nitro-2-(propan-2-ylsulfonyl)benzene (0.44 g, 1.6 mmol) and Dimethyl Phosphine oxide (0.15 g, 1.9 mmol) in 1 mL of DMF, was added Potassium Phosphate (0.37 g, 1.8 mmol), $\text{Pd}(\text{OAc})_2$ (18 mg, 0.08 mmol), Xantphos (55 mg, 0.10 mmol). The reaction mixture was stirred at 110 degrees C overnight. The reaction mixture was cooled to room temperature and filtered through celite. The desired product was isolated through prep-HPLC to yield a brownish yellow solid (0.24 g, 55% yield).

4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline

To a solution of dimethyl[4-nitro-3-(propan-2-ylsulfonyl)phenyl]phosphane oxide (0.24 g, 0.88 mmol) in Ethanol was added Pd on carbon (10% w/w, 24 mg) and stirred under hydrogen overnight. The reaction mixture was filtered and the organic solvent was removed under reduced pressure. The residue was purified by prep-HPLC to yield 100 mg of desired product (50% yield).

5-chloro-N-{2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazin-3-amine

To a solution of 5-chloro-6-methyl-1,2,4-triazin-3-amine (2.00 mmol) in 8 mL toluene is added 4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)aniline (2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and cesium carbonate (2.20 mmol). The mixture is purged with nitrogen, and can be subjected to microwaves at 100° C. until formation of the desired product. The reaction mixture can then be concentrated and purified by silica gel chromatography.

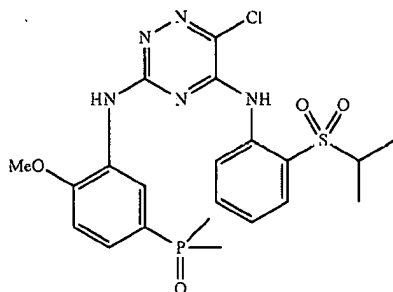
N^5 -[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]- N^3 -{2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine

To a solution of 5-chloro-N-{2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazin-3-amine (0.035 g, 0.11 mmol) in 1 mL of 2-methoxyethanol in a vial is added 2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]aniline (0.020 g, 0.085 mmol). The vial is sealed and the reaction is heated at 90° C. until formation of the desired compound. The reaction is then quenched with 1N NaOH solution and the solution extracted ethyl acetate. The organic layers are combined, washed with saturated sodium chloride solution, dried with sodium sulfate, filtered and concentrated. The crude residue is purified by silica gel chromatography.

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Example 112

6-chloro-N³-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



5-(Dimethylphosphoryl)-2-methoxyaniline

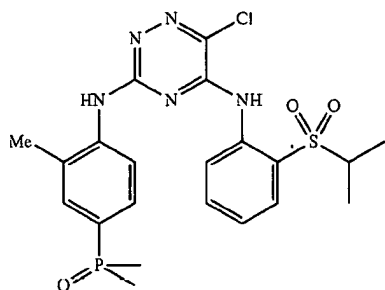
To a solution of 5-bromo-2-methoxyaniline (0.404 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.365 g, 85% yield).

6-chloro-N³-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 104; 0.7 mmol), 5-(Dimethylphosphoryl)-2-methoxyaniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na₂CO₃. The dichloromethane extract is dried over MgSO₄ and evaporated. The crude product is purified by Prep-HPLC.

Example 113

6-chloro-N³-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



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4-(Dimethylphosphoryl)-2-methylaniline

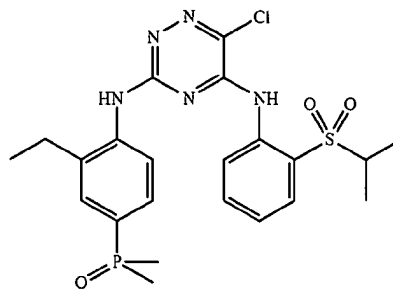
To a solution of 4-bromo-2-methylaniline (0.372 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.313 g, 85% yield).

6-chloro-N³-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106; 0.7 mmol), 4-(Dimethylphosphoryl)-2-methylaniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na₂CO₃. The dichloromethane extract is dried over MgSO₄ and evaporated. The crude product is purified by Prep-HPLC.

Example 114

6-chloro-N³-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



4-(Dimethylphosphoryl)-2-ethylaniline

To a solution of 4-bromo-2-ethylaniline (0.400 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.308 g, 78% yield).

6-chloro-N³-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

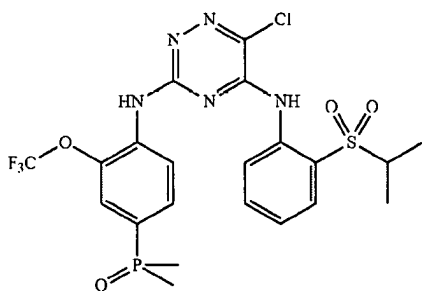
A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106;

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0.7 mmol), 4-(Dimethylphosphoryl)-2-ethylaniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 115

6-chloro- N^3 -[4 (dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



4-(Dimethylphosphoryl)-2-(trifluoromethoxy)aniline

To a solution of 4-iodo-2-(trifluoromethoxy)aniline (0.606 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150°C . for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) and acidified with HCl in methanol to afford the desired product as its hydrochloride salt (0.573 g, 98% yield).

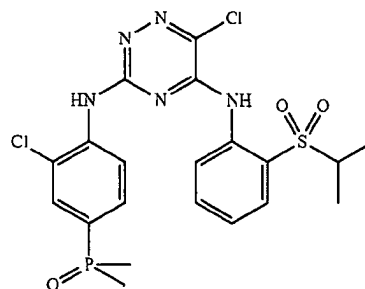
6-chloro- N^3 -[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro- N -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106; 0.7 mmol), 4-(Dimethylphosphoryl)-2-(trifluoroethoxy)aniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

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Example 116

6-chloro- N^3 -[2-chloro-4-(dimethylphosphoryl)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



2-Chloro-4-(dimethylphosphoryl)aniline

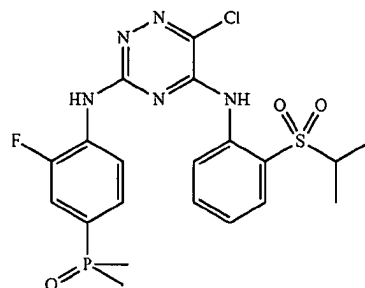
To a solution of 2-chloro-4-iodoaniline (0.507 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150°C . for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (0.340 g, 83% yield).

6-chloro- N^3 -[2-chloro-4-(dimethylphosphoryl)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro- N -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106; 0.7 mmol), 2-Chloro-4-(dimethylphosphoryl)aniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 117

6-chloro- N^3 -[4-(dimethylphosphoryl)-2-fluorophenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



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4-(Dimethylphosphoryl)-2-fluoroaniline

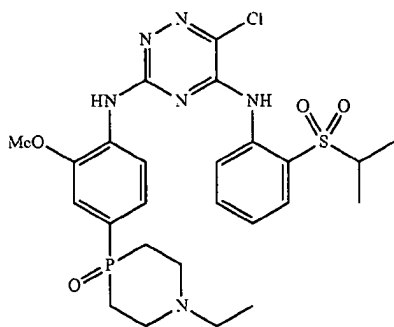
To a solution of 4-bromo-2-fluoroaniline (0.380 g, 2.00 mmol) in 8 mL DMF was added dimethylphosphine oxide (0.171 g, 2.20 mmol), palladium acetate (22.4 mg, 0.0100 mmol), XANTPHOS (69.4 mg, 0.120 mmol), and potassium phosphate (0.467 g, 2.20 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-20% 7N ammonia in methanol:dichloromethane) to afford the desired product (73.5 mg, 20% yield).

6-chloro-N³-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

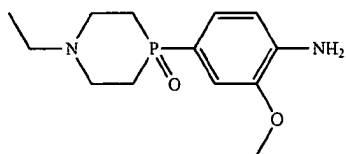
A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106; 0.7 mmol), 4-(Dimethylphosphoryl)-2-fluoroaniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na₂CO₃. The dichloromethane extract is dried over MgSO₄ and evaporated. The crude product is purified by Prep-HPLC.

Example 118

6-chloro-N³-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline



Diethyl (3-methoxy-4-nitrophenyl)phosphonate

To a solution of 5-chloro-2-nitroanisole (1.00 g, 5.33 mmol) in 20 mL DMF was added diethyl phosphite (0.809 g,

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5.86 mmol), palladium acetate (0.060 g, 0.27 mmol), XANTPHOS (0.185 g, 0.320 mmol), and potassium phosphate (1.24 g, 5.86 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-45% ethyl acetate:heptane) to afford the desired product (0.504 g, 33% yield).

(3-methoxy-4-nitrophenyl)phosphonic dichloride

To a solution of diethyl (3-methoxy-4-nitrophenyl)phosphonate (4.54 g, 15.7 mmol) in 1.2 mL DMF was added thionyl chloride (5.7 mL, 78.5 mmol). The reaction flask was equipped with a reflux condenser and the mixture was heated to reflux. After 2 h at reflux, the reaction was cooled to room temperature and concentrated in vacuo. The crude oil was redissolved in CH₂Cl₂ and heptane was added to precipitate the desired compound. The clear solution was decanted and the precipitate was collected and dried to afford the desired compound as a white solid (1.39 g, 33% yield).

Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide

To a solution of (3-methoxy-4-nitrophenyl)phosphonic dichloride (1.39 g, 5.15 mmol) in 15 mL THF at -78° C. under nitrogen was slowly added vinylmagnesium bromide (10.3 mL, 1.0 M in THF). After the addition was complete, the reaction stirred at -78° C. for an additional hour. The cold reaction mixture was quenched by the addition of saturated NH₄Cl (20 mL) and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with 1 M NaOH, brine, and dried over MgSO₄. The organic extracts were filtered and concentrated to provide Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.982 g, 75%).

1-ethyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide

Diethenyl(3-methoxy-4-nitrophenyl)phosphane oxide (0.480 g, 1.94 mmol), ethylamine hydrochloride (0.174 g, 2.12 mmol), and 1 N NaOH (2 mL) were dissolved in 50% aqueous THF (5 mL) and heated to 105° C. under nitrogen. After one hour, another portion of benzylamine was added to the reaction mixture. The reaction mixture was refluxed for an additional 2 h. and then cooled to room temperature. The reaction mixture was partitioned between saturated aqueous NaHCO₃ and CH₂Cl₂. The aqueous phase was washed once with CH₂Cl₂ and the organic layers were combined. The organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the compound (0.267 g, 46% yield).

4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline

To a solution of 1-ethyl-4-(3-methoxy-4-nitrophenyl)-1,4-azaphosphinane 4-oxide (0.267 g, 0.895 mmol) in 5 mL ethanol was added 10% Pd/C (27 mg) and 2.5 M HCl in ethanol (1.43 mL). The flask was equipped with a septum, evacuated, and refilled with hydrogen. The flask was equipped with a hydrogen balloon and the reaction stirred for 3 h. The flask was then evacuated and refilled with nitrogen. The reaction mixture was filtered through Celite and concentrated to pro-

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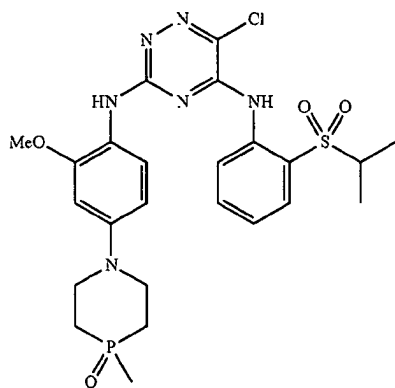
vide the crude compound as the hydrochloride salt, which was used without purification.

6-chloro-N³-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

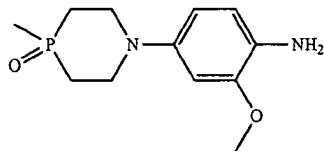
A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106: 0.7 mmol), 4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyaniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na₂CO₃. The dichloromethane extract is dried over MgSO₄ and evaporated. The crude product is purified by Prep-HPLC.

Example 119

6-chloro-N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline



1-benzyl-4-methyl-1,4-azaphosphinane 4-oxide

To a solution of methylphosphonic dichloride (10.0 g, 75.2 mmol) in CH₂Cl₂ at -78° C., was added vinylmagnesium bromide (175 mL, 1.0 M in THF) via addition funnel over 4 h. The solution was warmed to 0° C. and quenched with a minimum amount of saturated NH₄Cl. The mixture was filtered through a pad of silica gel and silica was extracted with 10% 7N ammonia in methanol:dichloromethane. The solution was concentrated under reduced pressure to afford methyl divinyl phosphine oxide as a viscous, yellow oil that was used without purification.

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A solution of methyl divinyl phosphine oxide (1.16 g, 10.0 mmol) and benzylamine (1.20 mL, 11.0 mmol) in 1:1 THF/water (25 mL) was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford 1-benzyl-4-methyl-[1,4]azaphosphinane-4-oxide as a white solid (1.57 g, 70% yield).

4-methyl-[1,4]azaphosphinane-4-oxide

A flask was charged with 1-benzyl-4-methyl-[1,4]azaphosphinane-4-oxide (1.00 g, 4.47 mmol) and 10% Pd/C (100 mg). The flask was evacuated and filled with nitrogen. Anhydrous methanol (18 mL) was added to the flask and the flask was equipped with a reflux condenser with a nitrogen inlet. Ammonium formate (2.25 g, 35.8 mmol) was added in one portion at room temperature. The resulting mixture was stirred at reflux for 2 h. The reaction was filtered through a Celite pad and the Celite was washed with 2x5 mL methanol. The combined filtrate and washing was evaporated in vacuo. The crude residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford 4-methyl-[1,4]azaphosphinane-4-oxide as a yellow gel (0.589 g, 99% yield).

1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide

A mixture of 4-methyl-[1,4]azaphosphinane-4-oxide (133 mg, 1.00 mmol), 5-fluoro-2-nitroanisole (340 mg, 2.00 mmol), K₂CO₃ (345 mg, 2.50 mmol), and DMF (5 mL) was heated to 50° C. After 2 h, the reaction mixture was concentrated and purified by silica gel chromatography (0-5% 7N ammonia in methanol:dichloromethane) to afford 1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide as a bright yellow solid (272 mg, 96% yield).

2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline

To a pressure vessel was added 1-(3-methoxy-4-nitrophenyl)-4-methyl-1,4-azaphosphinane 4-oxide (272 mg, 0.960 mmol), ethanol (5 mL), and 10% Pd/C (50 mg). The vessel was connected to a Parr apparatus, evacuated, and refilled with nitrogen. The vessel was then evacuated and filled with hydrogen gas to a pressure of 50 psi. The reaction mixture was shaken under 50 psi for 4 h. The mixture was filtered through Celite to a flask containing HCl in ethanol. Concentration of the filtrate afforded 2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline as a gray solid (211 mg, 87% yield).

6-chloro-N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

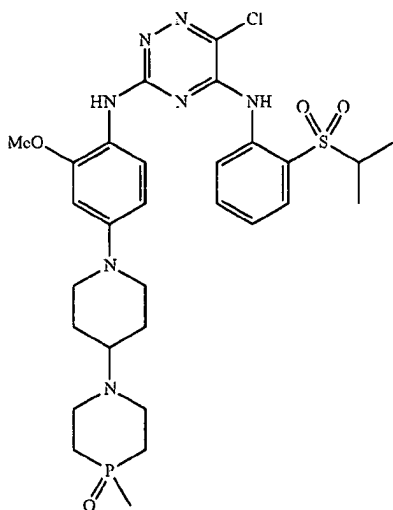
A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106: 0.7 mmol), 2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)aniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous

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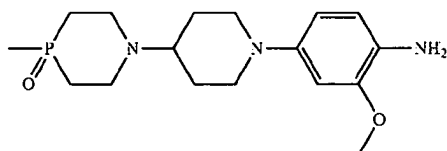
solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

Example 120

6-chloro- N^3 -{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline



tert-butyl 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidine-1-carboxylate

A solution of methyl divinyl phosphine oxide (140 mg, 1.21 mmol) and 1-Boc-4-aminopiperidine (265 mg, 1.33 mmol) in 1:1 THF/water (3 mL) was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the desired compound as a white solid (178 mg, 38% yield).

1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methyl-1,4-azaphosphinan-4-oxide

To a stirring solution of tert-butyl 4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidine-1-carboxylate (178 mg, 0.563 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid

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(0.5 mL). After 20 min, the solution was concentrated and the resulting residue was redissolved in DMF (2 mL). Potassium carbonate (160 mg, 1.16 mmol) was added portionwise to the stirring solution followed by 5-fluoro-2-nitroanisole (158 mg, 0.930 mmol). The reaction mixture was heated to 50° C. After 2 h, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (0-10% 7N ammonia in methanol:dichloromethane) to afford the compound as a bright yellow solid (176 mg, 86% yield).

2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline

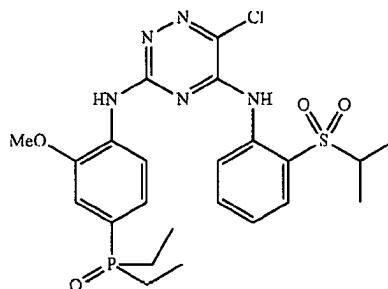
To a pressure vessel was added 1-[1-(3-methoxy-4-nitrophenyl)piperidin-4-yl]-4-methyl-1,4-azaphosphinan-4-oxide (176 mg, 0.485 mmol), ethanol (5 mL), and 10% Pd/C (50 mg). The vessel was connected to a Parr apparatus, evacuated, and refilled with nitrogen. The vessel was then evacuated and filled with hydrogen gas to a pressure of 50 psi. The reaction mixture was shaken under 50 psi for 4 h. The mixture was filtered through Celite to a flask containing HCl in ethanol. Concentration of the filtrate afforded the compound as a gray solid (178 mg, 98% yield).

6-chloro- N^3 -{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-5-amine (prepared as in Example 106; 0.7 mmol), 2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]aniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na_2CO_3 . The dichloromethane extract is dried over MgSO_4 and evaporated. The crude product is purified by Prep-HPLC.

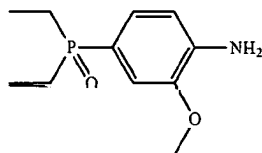
Example 121

6-chloro- N^3 -[4-(diethylphosphoryl)-2-methoxyphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine



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4-(Diethylphosphoryl)-2-methoxyaniline



To a solution of 4-bromo-2-methoxyaniline (0.100 g, 0.495 mmol) in 2 mL DMF was added diethylphosphine oxide (0.0730 g, 0.544 mmol), palladium acetate (5.6 mg, 0.025 mmol), XANTPHOS (17.2 mg, 0.030 mmol), and potassium phosphate (0.116 g, 0.544 mmol). The mixture was purged with nitrogen, and subjected to microwaves at 150° C. for 20 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (0-12% 7N ammonia in methanol:dichloromethane) and the fractions were concentrated. The residue was acidified with 2.5 M HCl in ethanol and the solution was concentrated to provide 4-(diethylphosphoryl)-2-methoxyaniline as the hydrochloride salt (0.132 g, 91% yield).

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6-chloro-N³-[4-(diethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine

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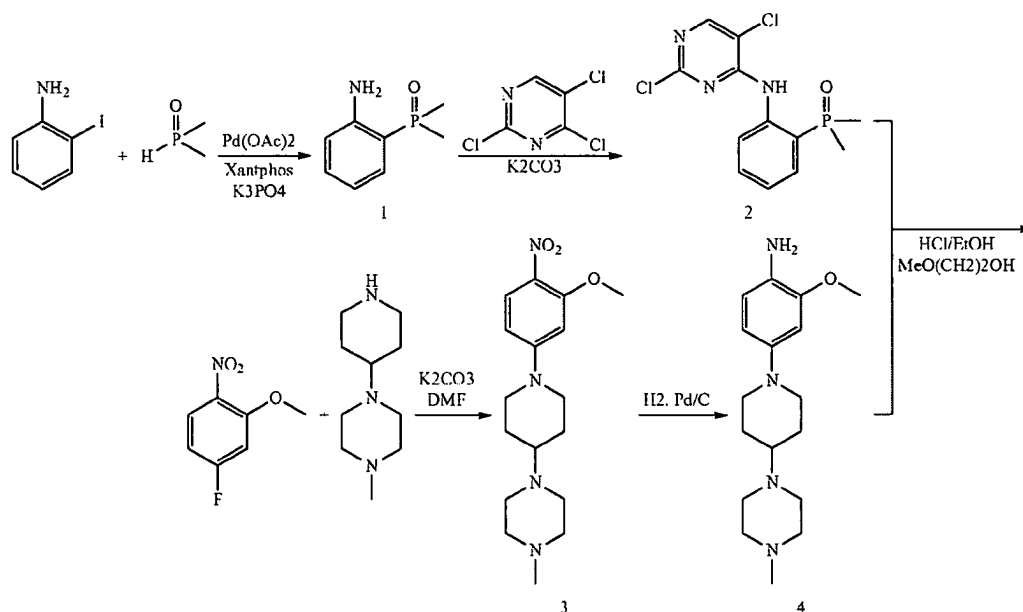
A mixture of 3,6-dichloro-N-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazin-5-amine (prepared as in Example 106; 0.7 mmol), 4-(Diethylphosphoryl)-2-methoxyaniline (0.7 mmol) and camphorsulfonic acid (0.7 equiv.), is refluxed for 20-48 hours in 2-propanol. The reaction mixture is allowed to cool to room temperature, dissolved in dichloromethane and washed with an aqueous solution of Na₂CO₃. The dichloromethane extract is dried over MgSO₄ and evaporated. The crude product is purified by Prep-HPLC.

Example 122

Synthesis of Compound 5

Compound 5 can be synthesized as outlined in Scheme 122 (below).

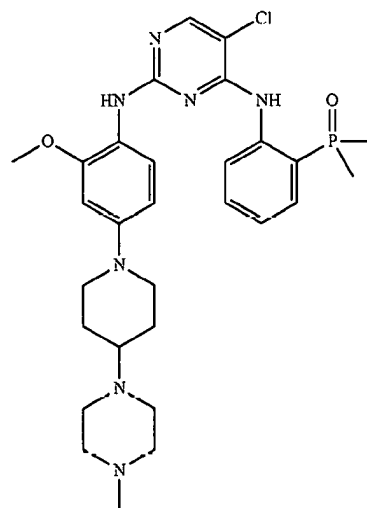
Scheme 122



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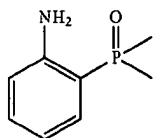
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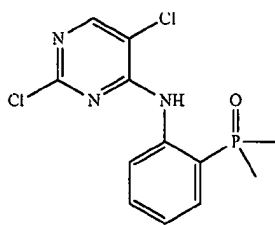
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Synthesis of 1



To a solution of 2-iodoaniline (1.0 eq) and dimethylphosphine oxide (1.1 eq) in DMF were added potassium phosphate (1.1 eq), palladium acetate/Xantphos (catalytic). The reaction was stirred at 150° C. for 3 hours and cooled to room temperature. The solvent was evaporated and the residue was worked up with DCM/water. The crude product was purified with a column (EtOAc/MeOH 10:1) to give 1 as a brown solid (80% yield).

Synthesis of 2



2,4,5-Trichloropyrimidine (1.57 eq), 1 (1.0 eq), and potassium carbonate (3.14 eq) in DMF were stirred at 60° C. for 5 hours and then cooled to r.t. The mixture was filtered and the filtrate was concentrated. The residue was purified with ISCO (DCM/MeOH 20:1) to give 2 as a yellow solid (61% yield).

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Synthesis of 3

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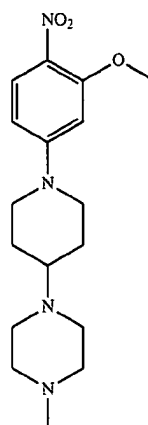
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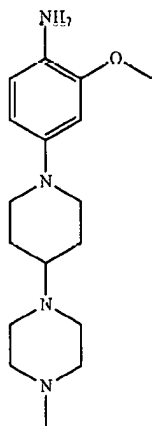
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5-Fluoro-2-nitroanisole (1.0 eq), 1-methyl-4-(piperidin-4-yl)piperazine (1.0 eq), and potassium carbonate (2.0 eq) in DMF were stirred at 120° C. for 6 hours and then cooled to r.t. The mixture was filtered and evaporated. The crude product was crystallized from ethanol to give 3 as a yellow solid (72% yield).

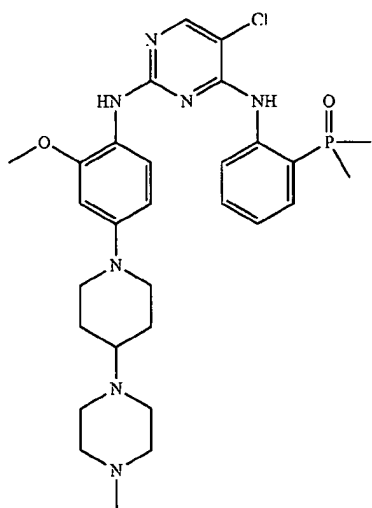
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Synthesis of 4



Palladium on activated carbon was added to a solution of 3 in ethanol under nitrogen. The suspension was then shaken under hydrogen (50 psi) for 3 hours. The mixture was filtered and the filtration was evaporated to give 4 as a purple solid in a quantitative yield.

Synthesis of 5



A solution of 2 (1.0 eq), 4 (1.4 eq), and 2.5 M HCl in ethanol (excess) in 2-methoxyethanol was sealed and heated at 120°C. with stirring for 5.5 hours and then cooled to r.t. The reaction was repeated 5 times and combined. The mixture was filtered and evaporated. Saturated Na₂CO₃ was added, followed by DCM with stirring strongly. The layers were separated and the aqueous layer was extracted with DCM. The organics were dried, evaporated and chromatographed

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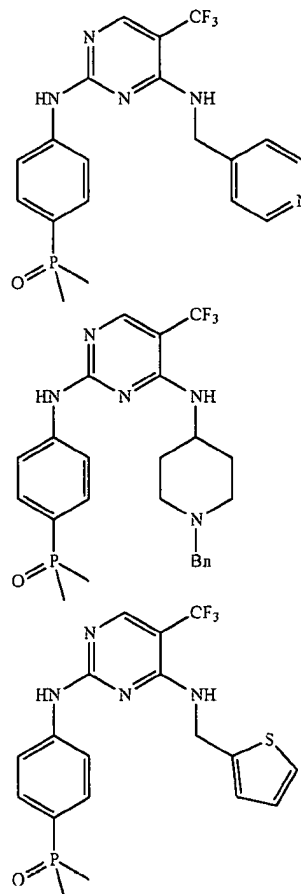
[EtOAc/MeOH (7M ammonia) 20:1] to give a yellow solid. EtOAc was added and the suspension was refluxed for 30 minutes. After cooled to r.t., filtration gave a solid, which was dissolved in DCM, filtered, and evaporated to afford 5 as an off-white solid (66% yield).

Example 123

Biological Evaluation of Compounds

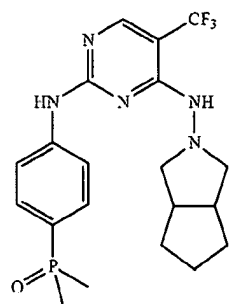
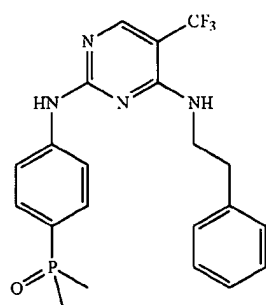
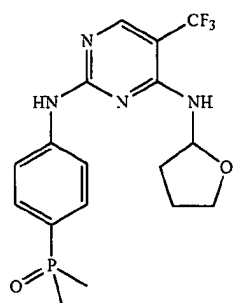
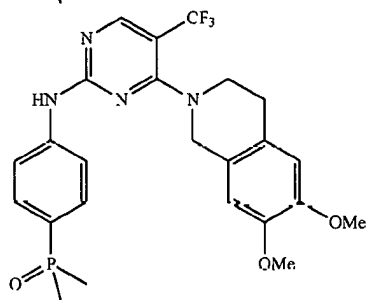
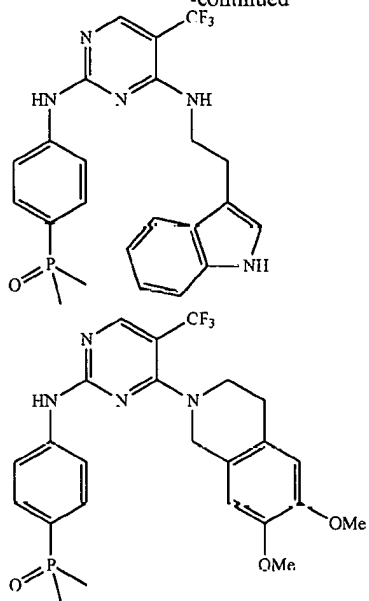
Compounds of the invention are evaluated in a variety of assays to determine their biological activities. For example, compounds of the invention can be tested for their ability to inhibit various protein kinases of interest. Some of the compounds tested displayed potent nanomolar activity against the following kinases: ALK and c-Met. Furthermore, some of these compounds were screened for antiproliferative activity in the human Karpas-299 and in the human SU-DHL-1 lymphoma cell lines and demonstrated activity on the range of 1-100 nM. The compounds can also be evaluated for their cytotoxic or growth inhibitory effects on tumor cells of interest, e.g., as described in more detail below and as shown above for some representative compounds. See e.g., WO 03/000188, pages 115-136, the full contents of which are incorporated herein by reference.

Some representative compounds of the invention are depicted below:

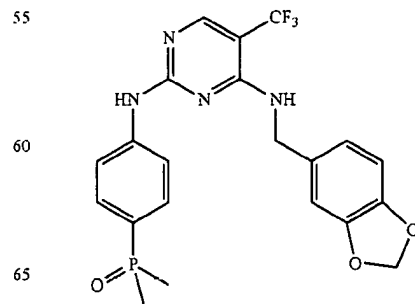
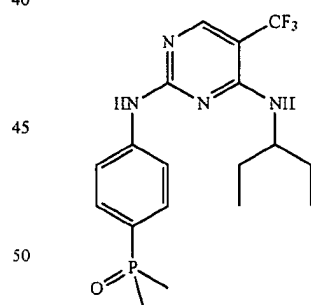
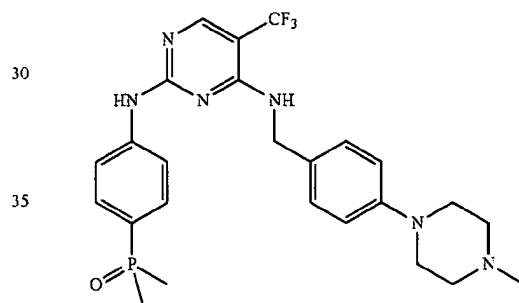
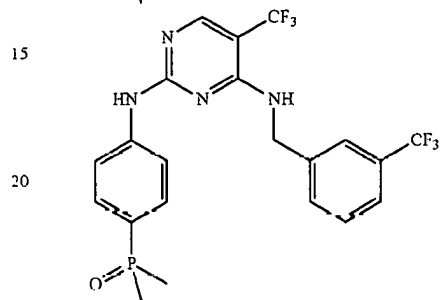
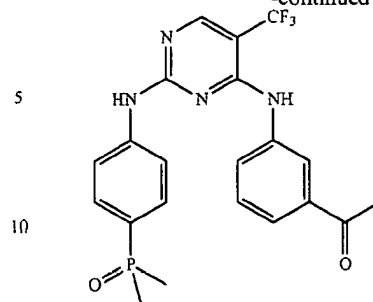


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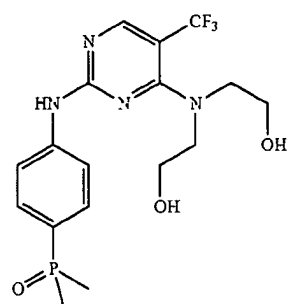
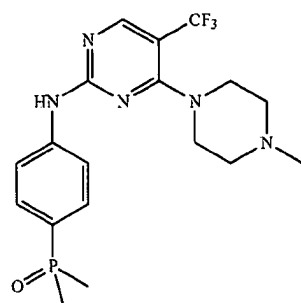
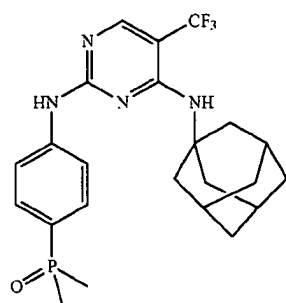
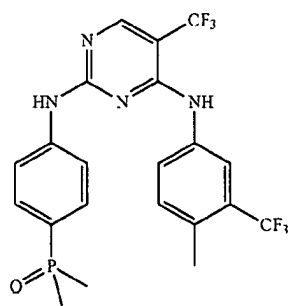
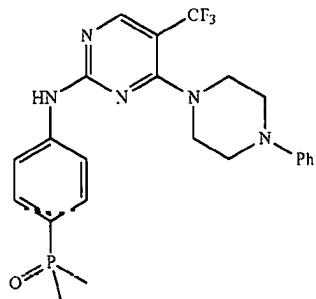
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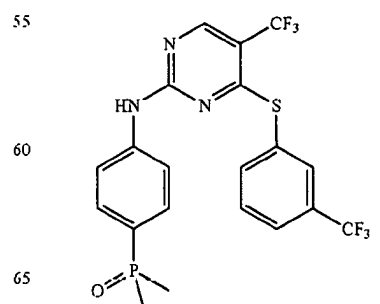
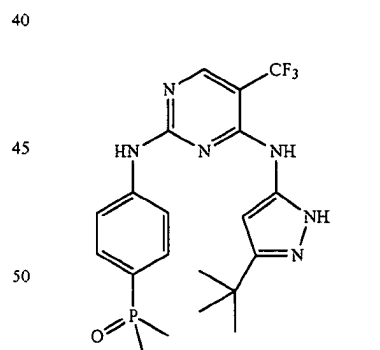
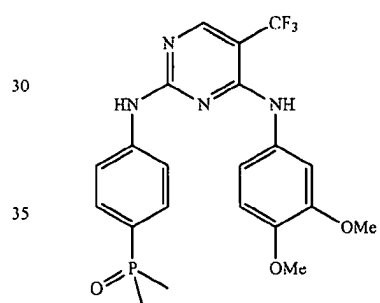
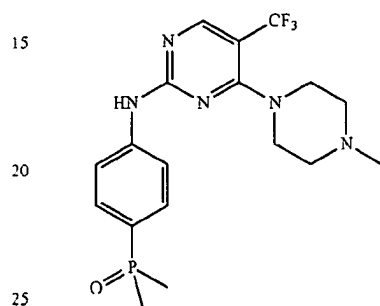
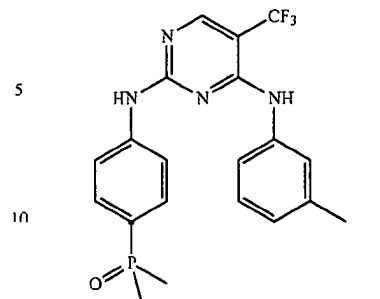


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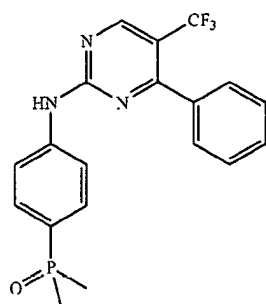
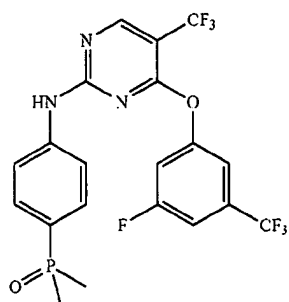
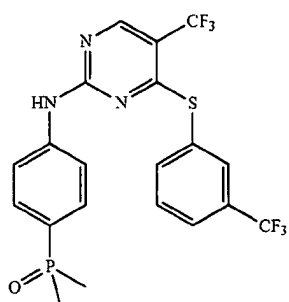
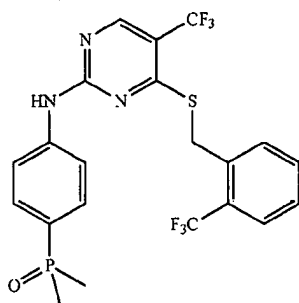
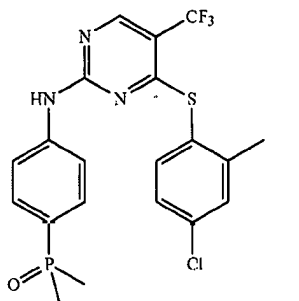
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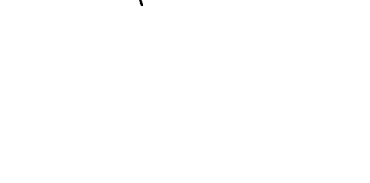
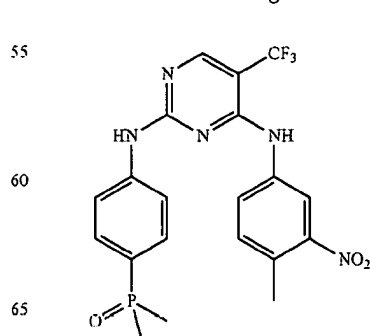
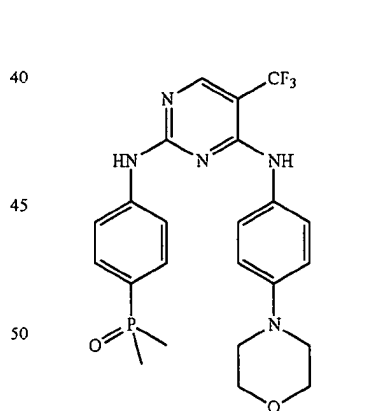
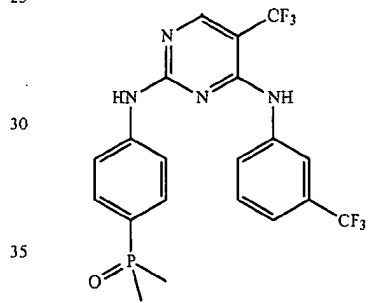
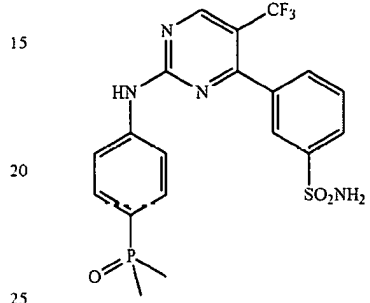
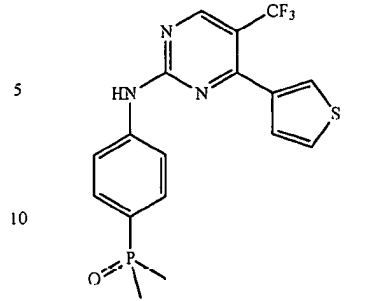
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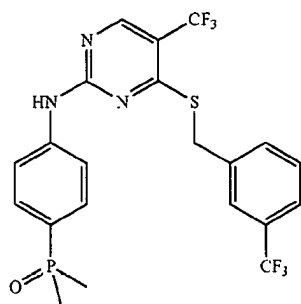
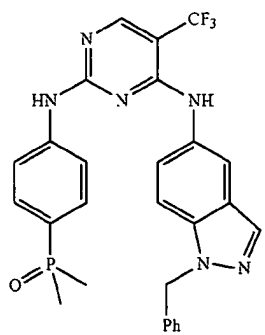
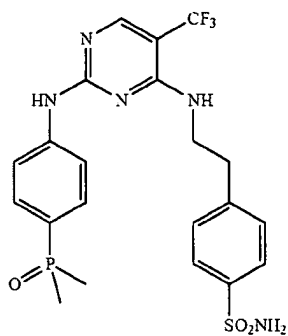
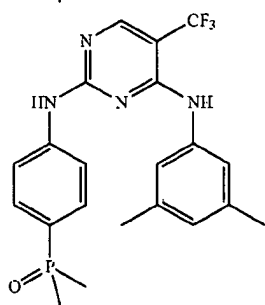
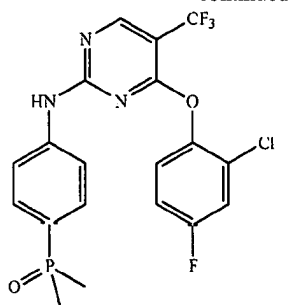
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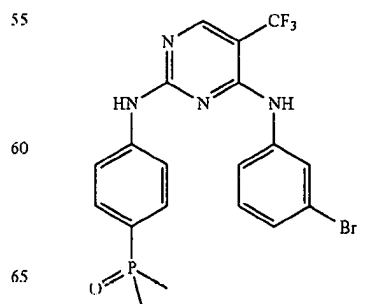
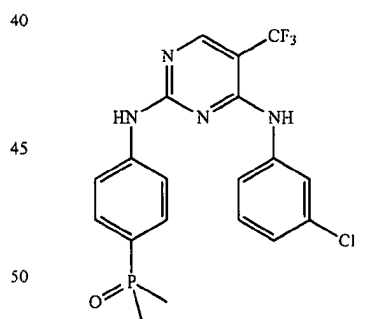
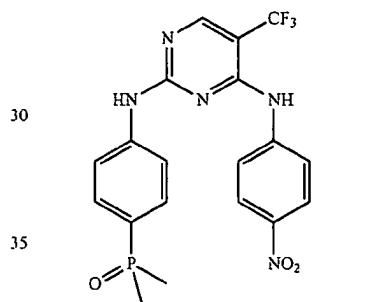
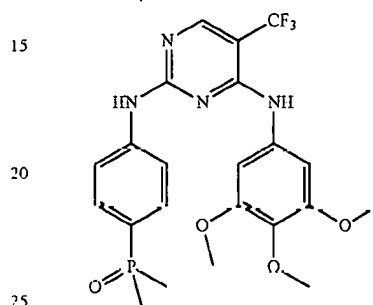
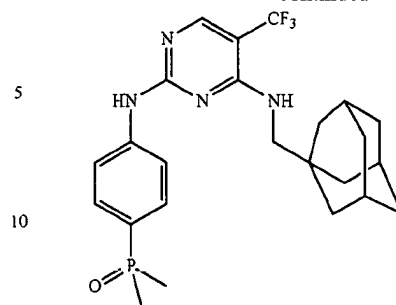
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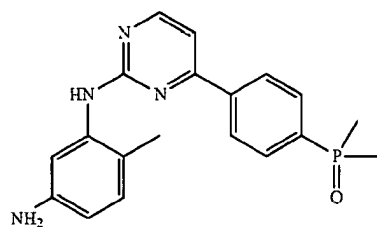
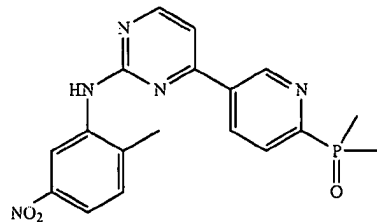
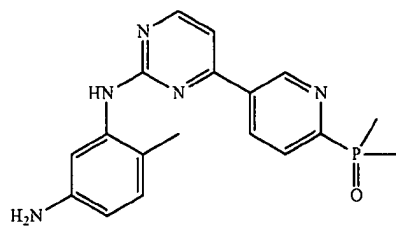
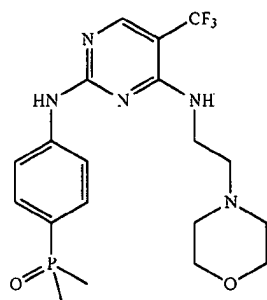
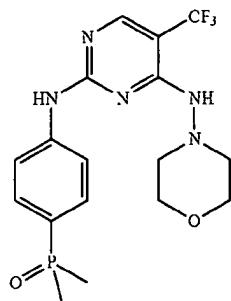
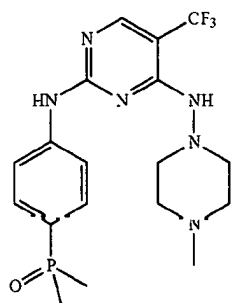
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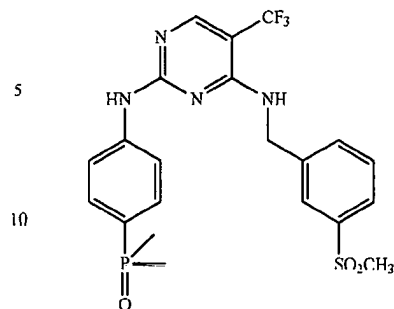
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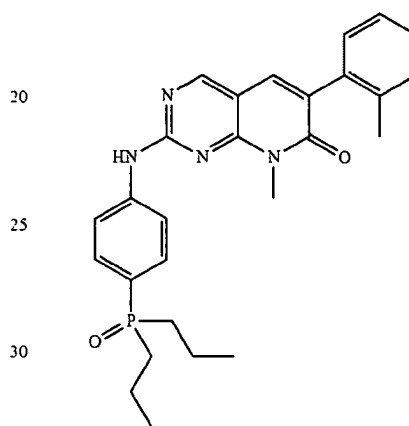


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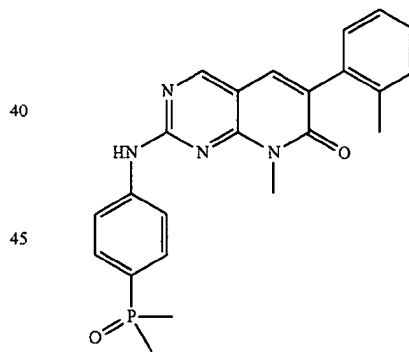
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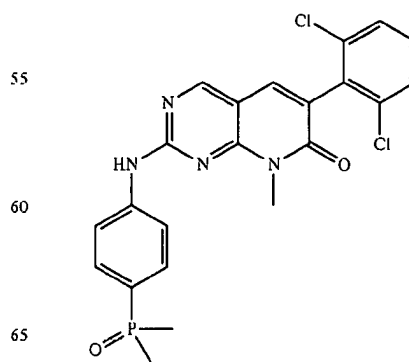
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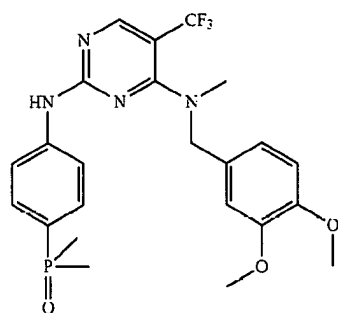
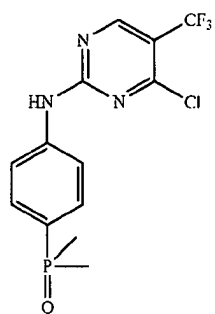
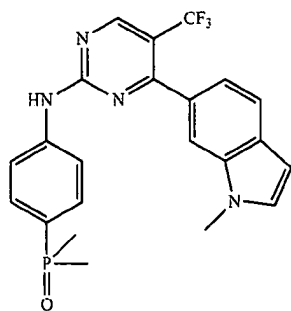
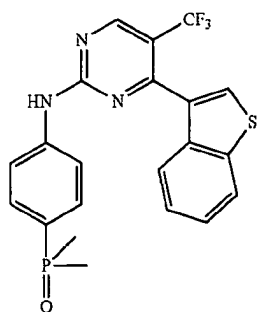
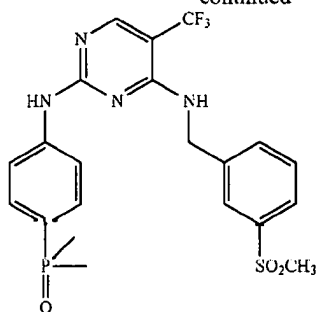
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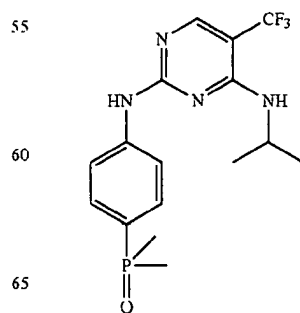
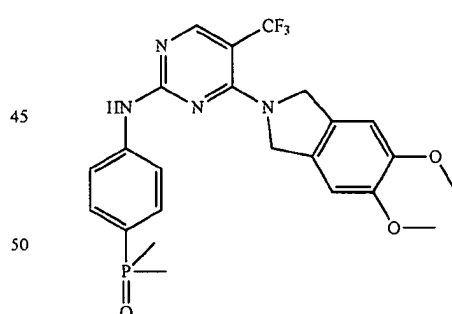
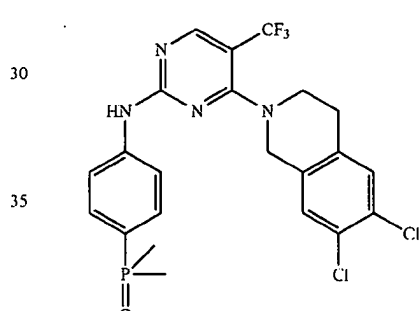
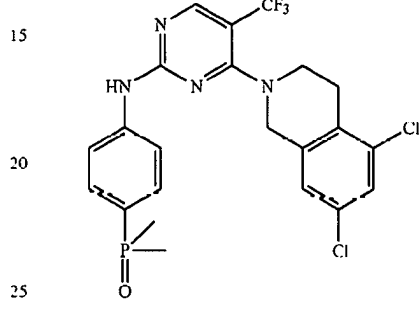
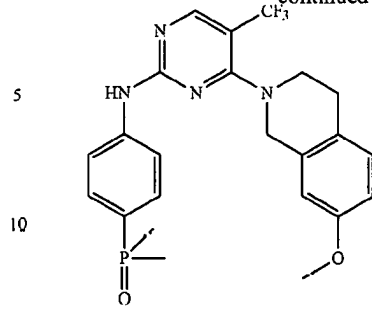
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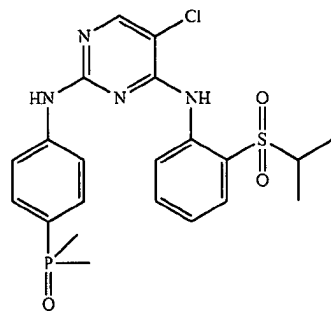
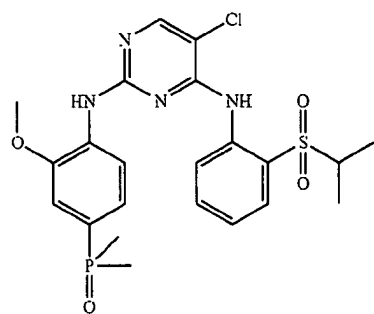
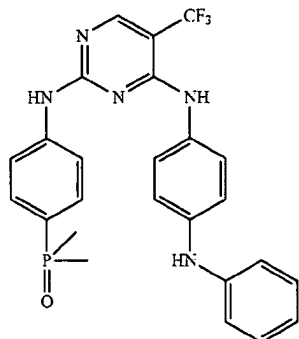
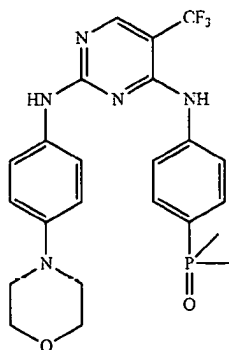
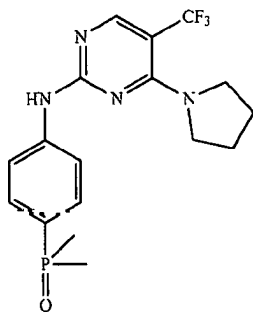
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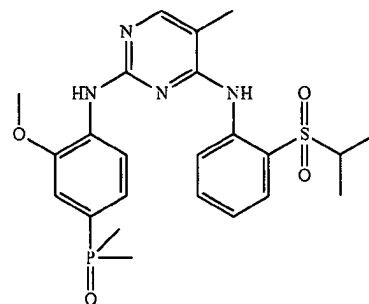
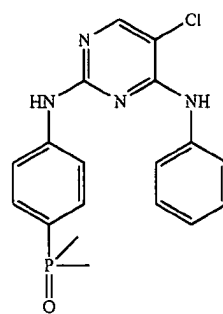
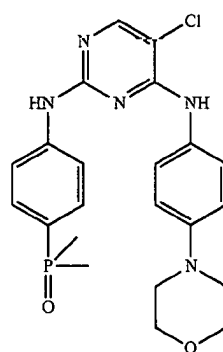
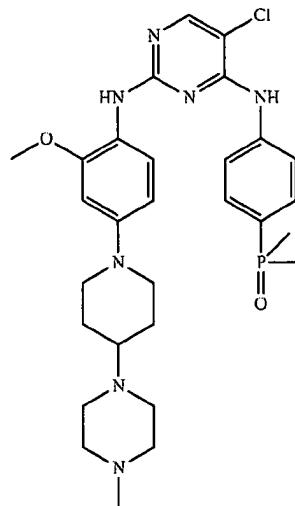
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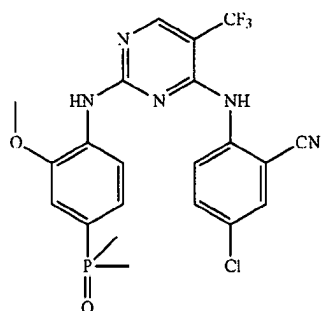
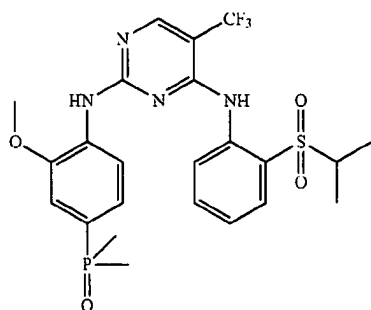
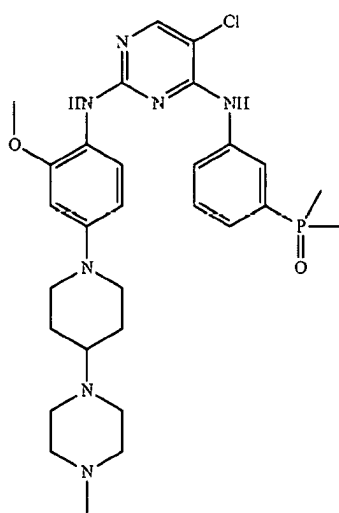
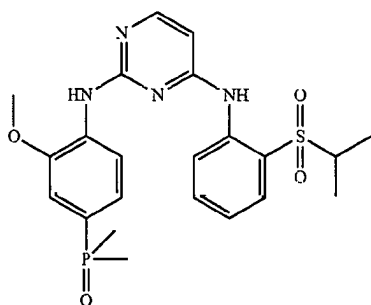
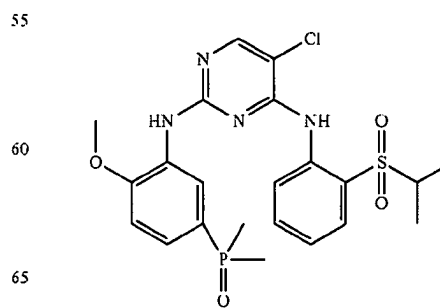
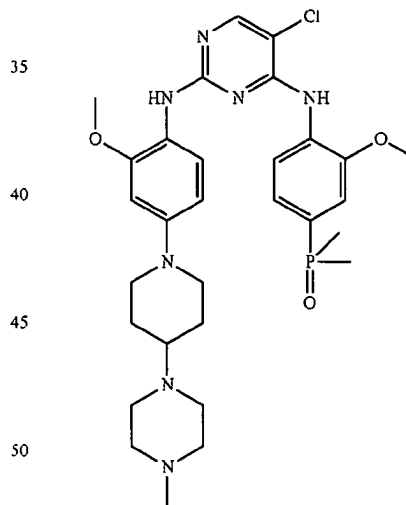
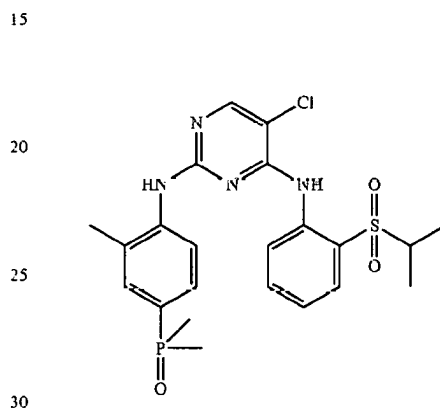
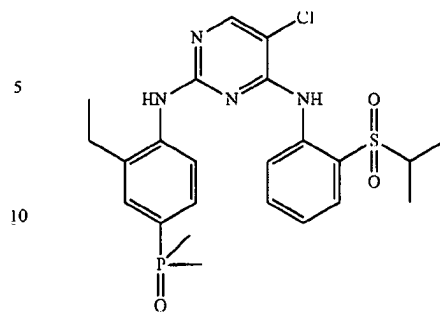
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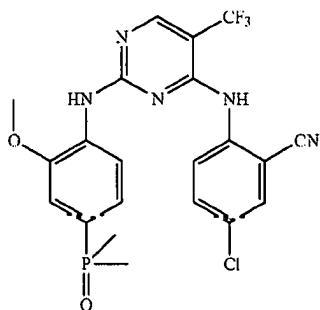
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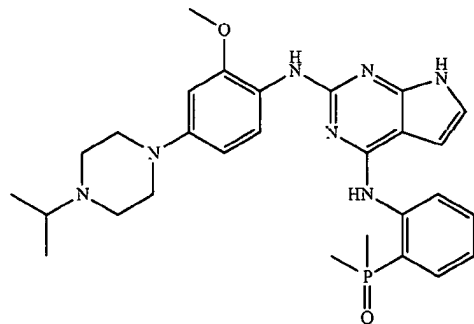
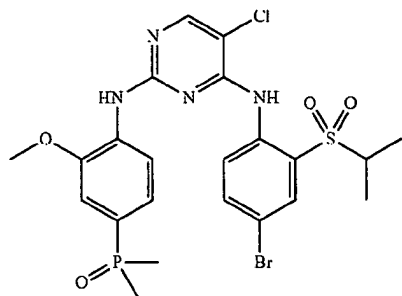
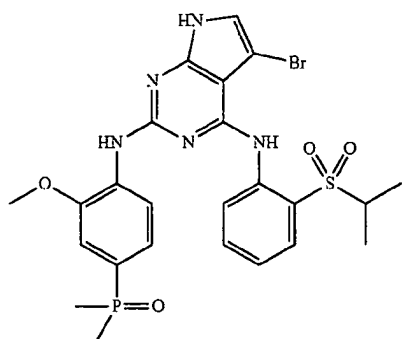
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The following representative compounds were synthesized and tested for kinase inhibition against a panel of kinases and some also tested in various cell lines. Many of the compounds were found to be active in in vitro assays.

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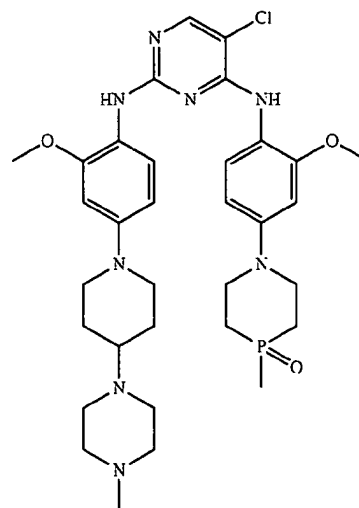
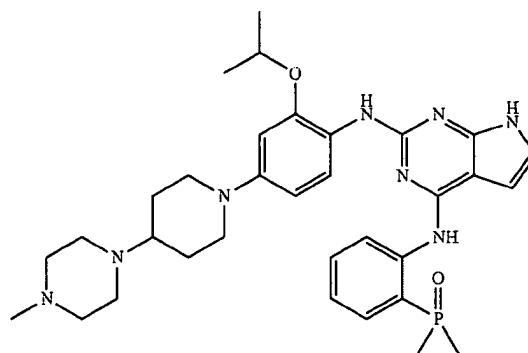
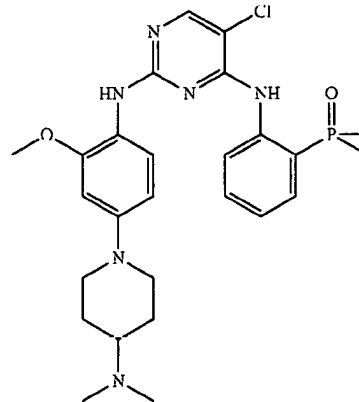
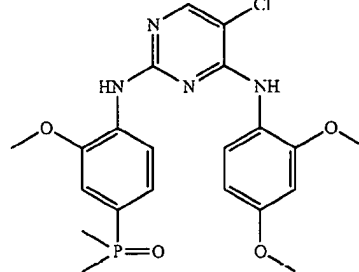
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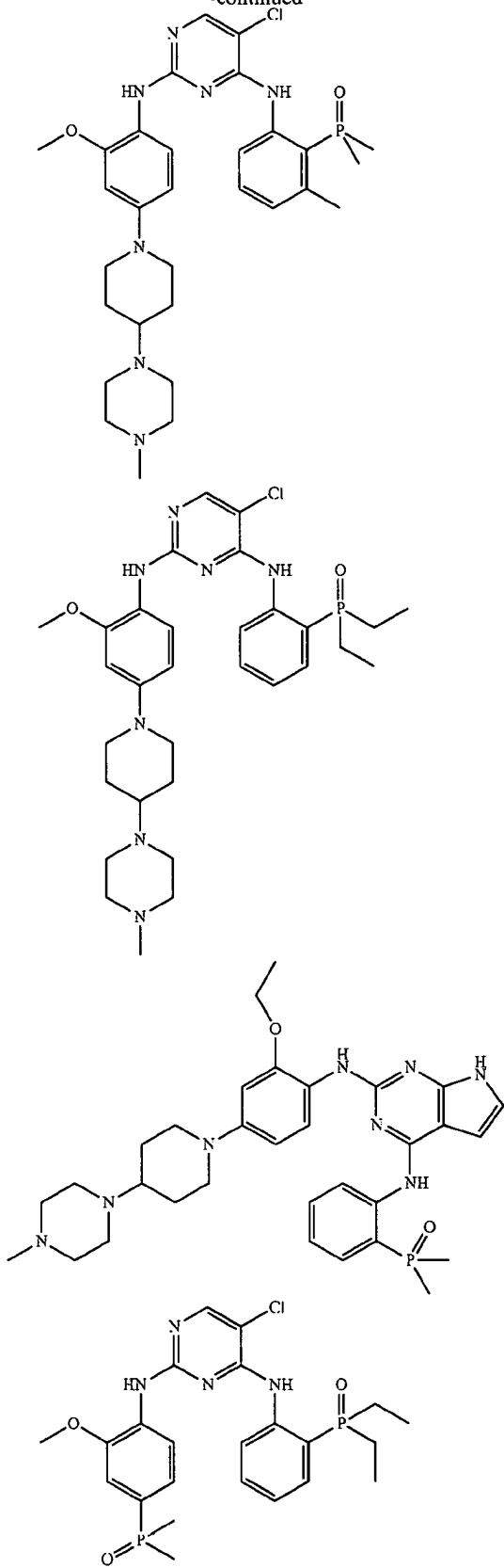
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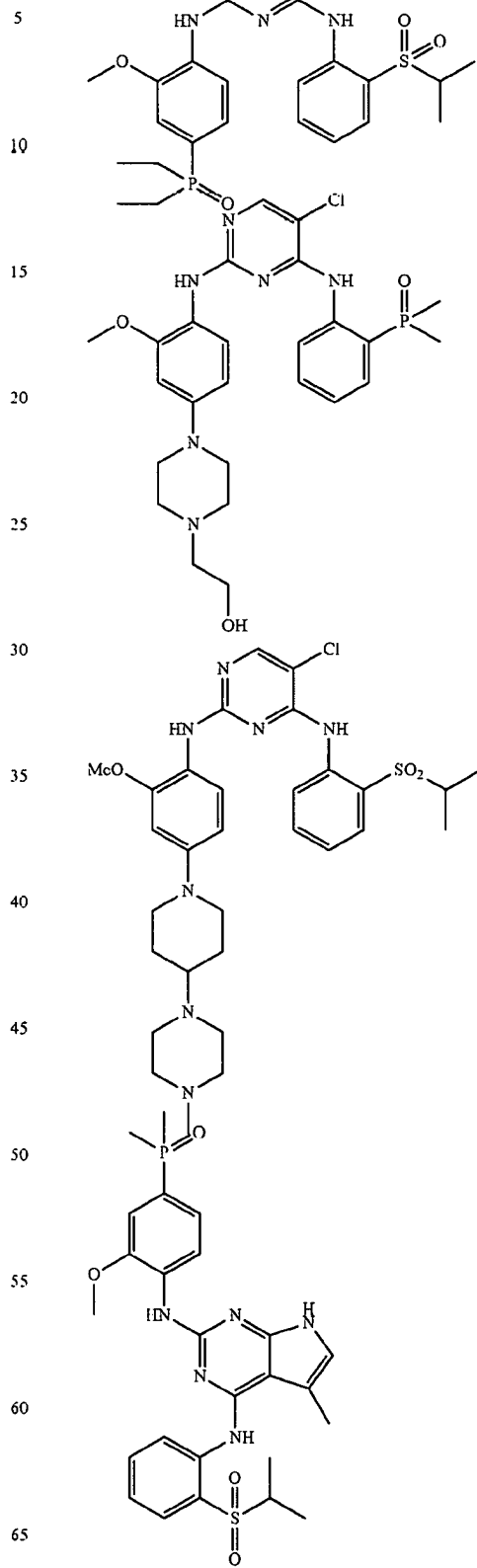
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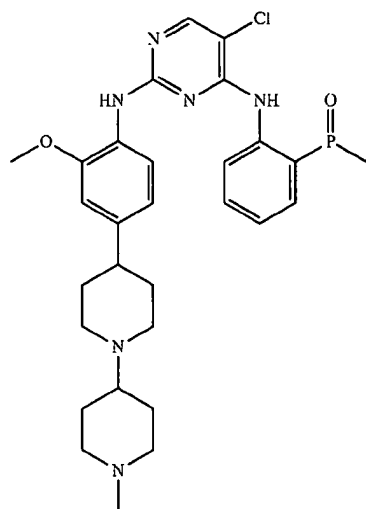
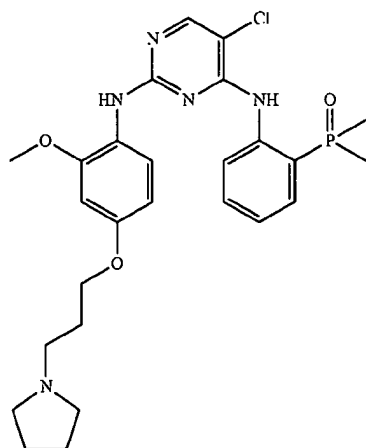
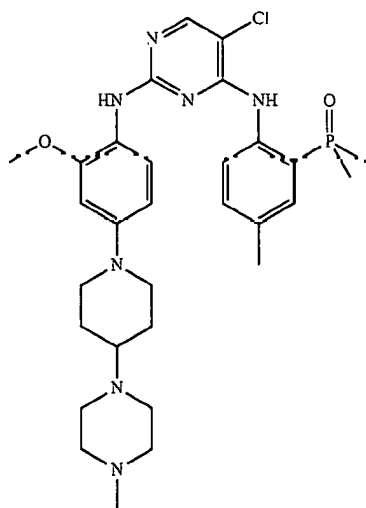


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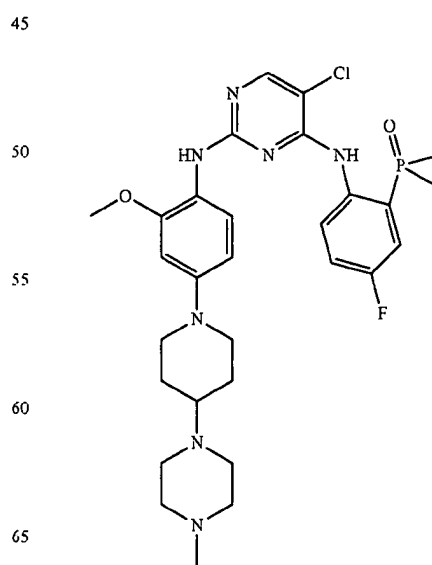
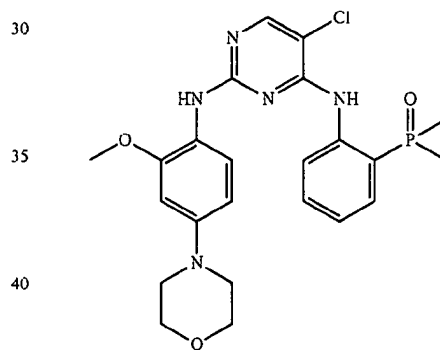
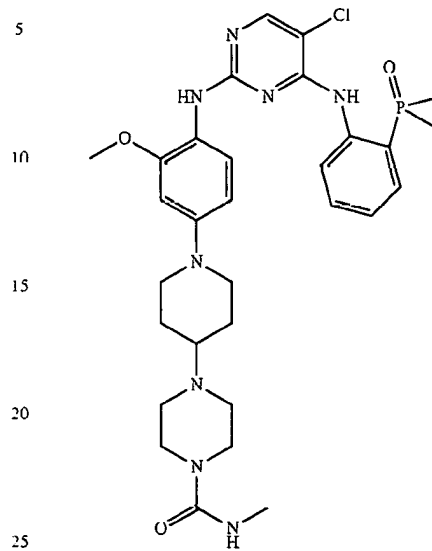
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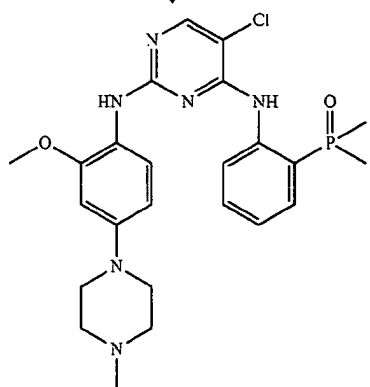
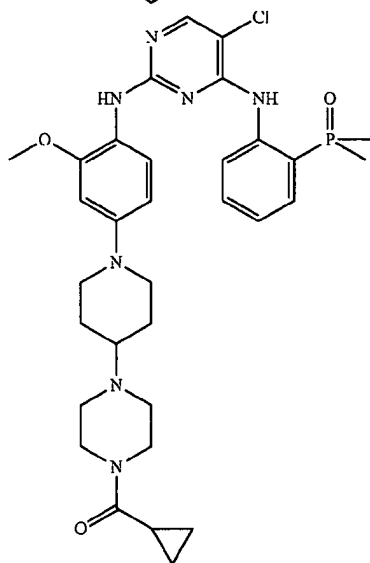
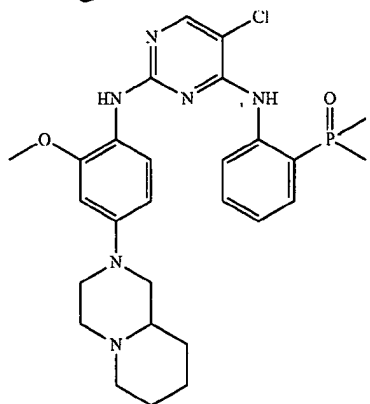
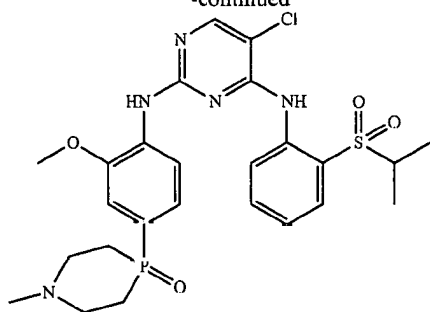


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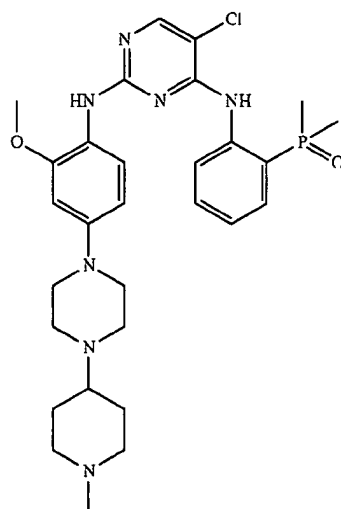
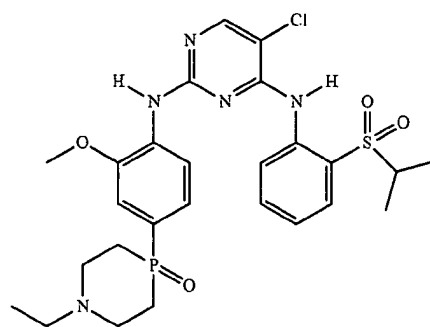
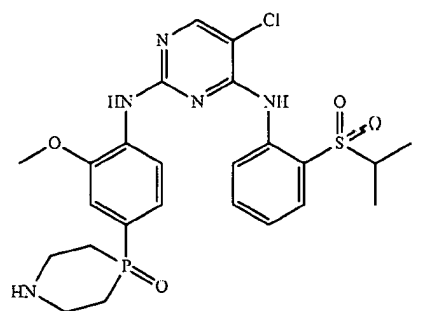
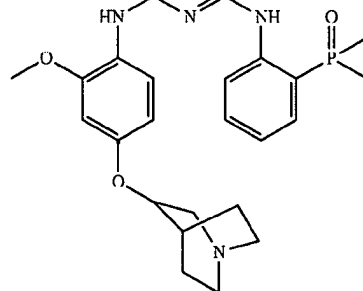
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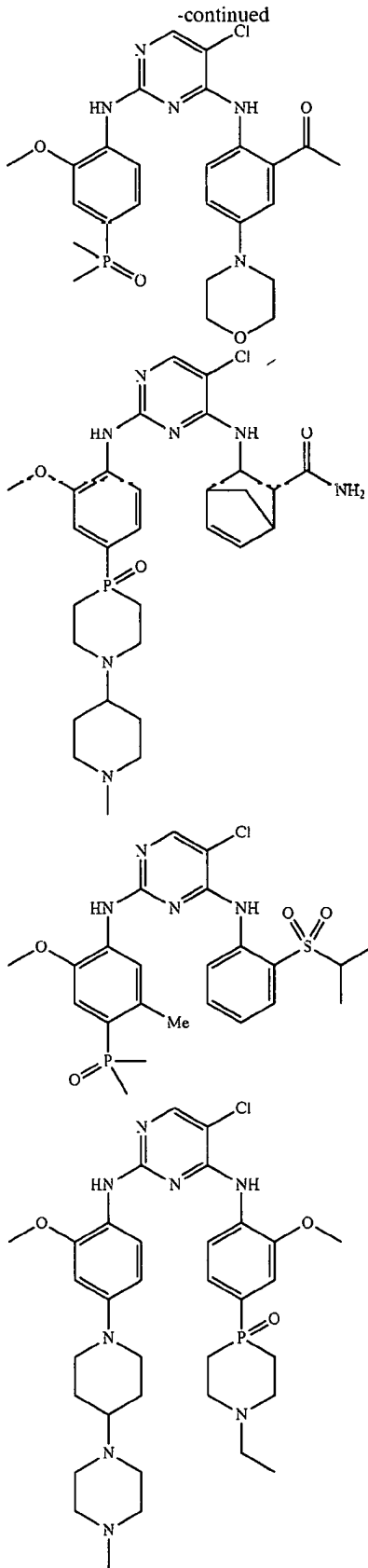
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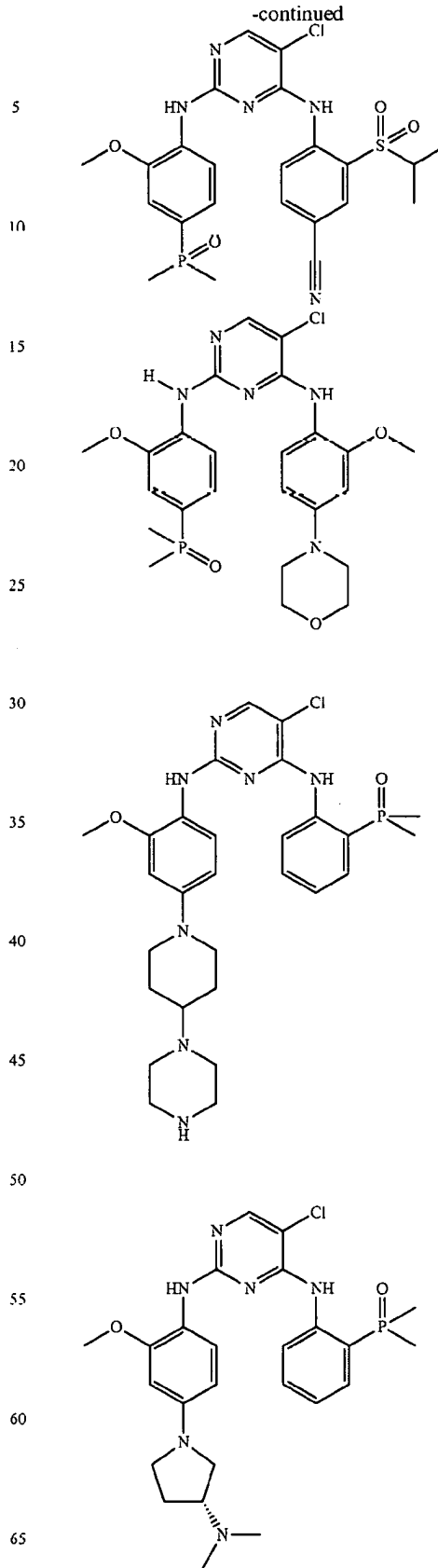
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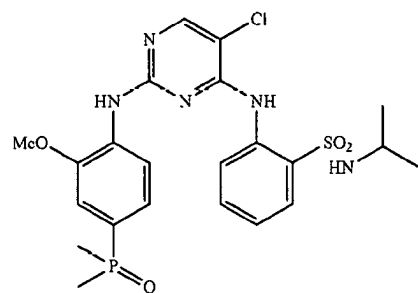
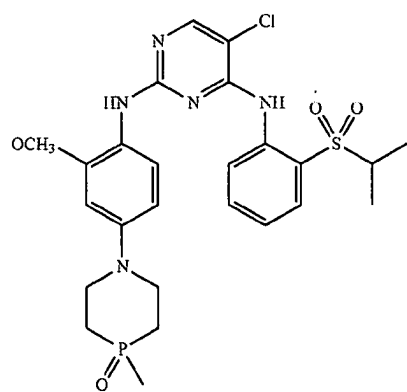
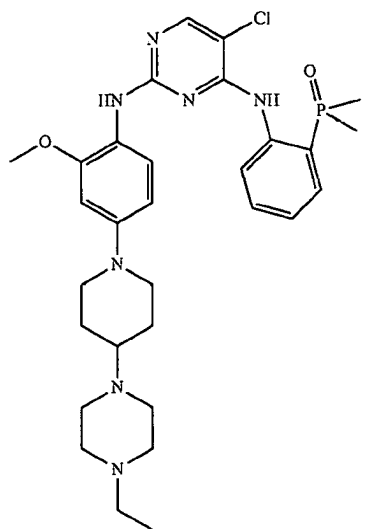
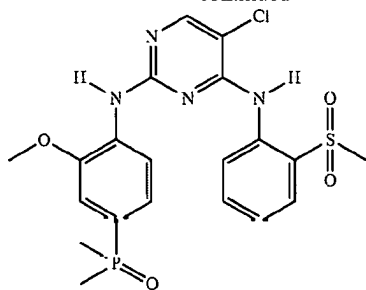
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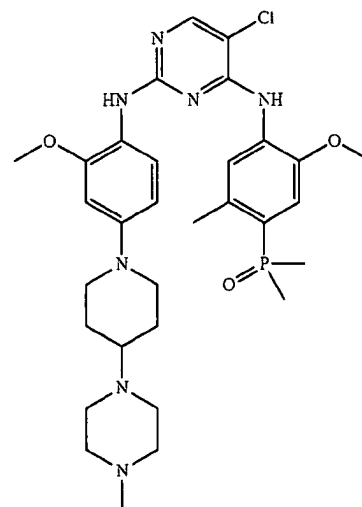
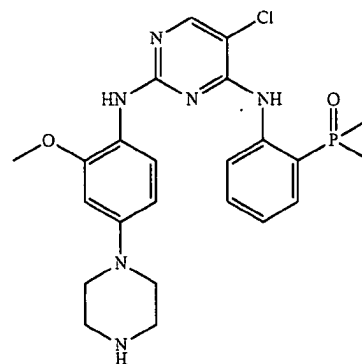
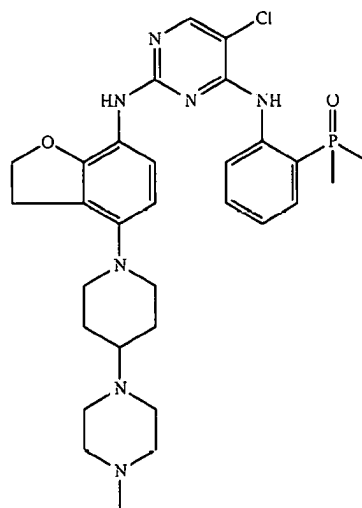
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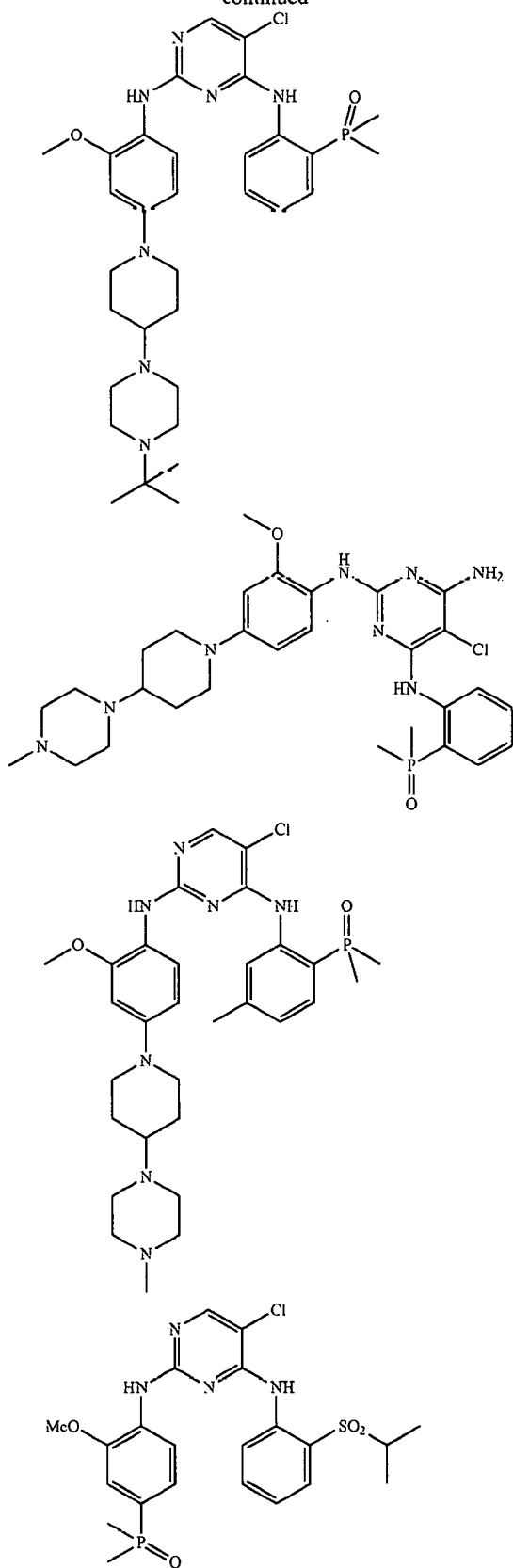
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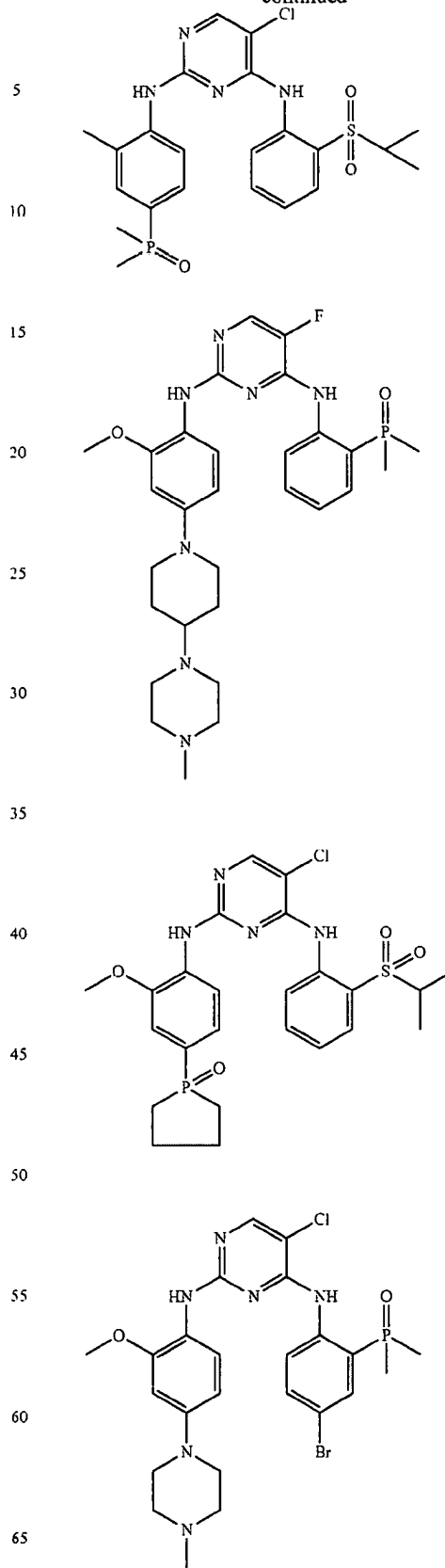
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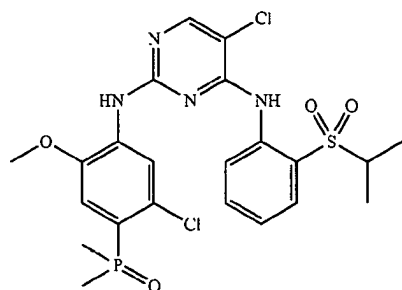
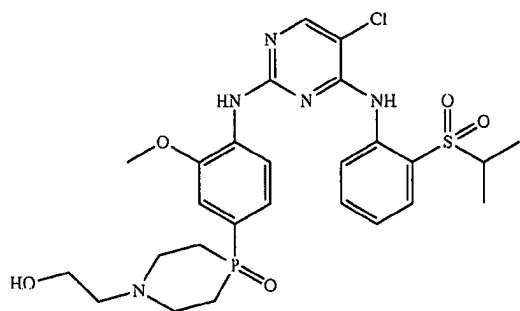
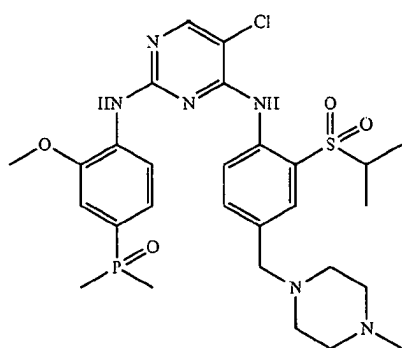
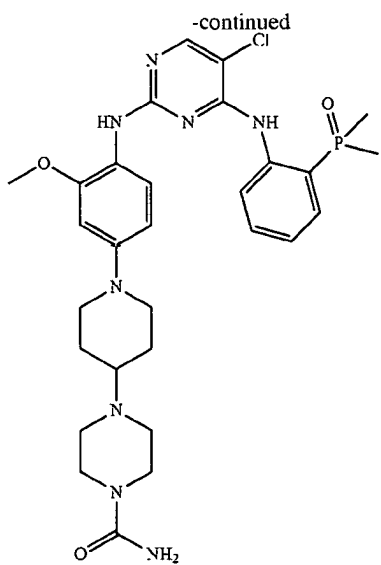
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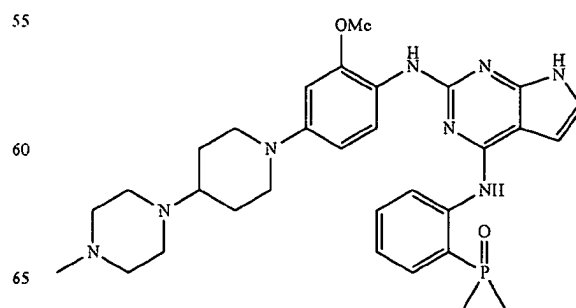
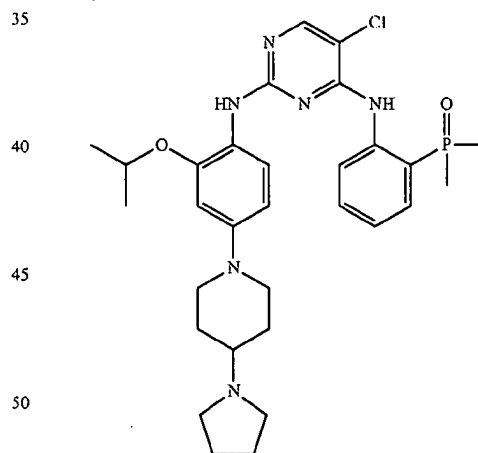
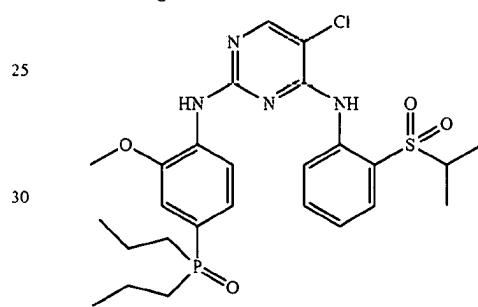
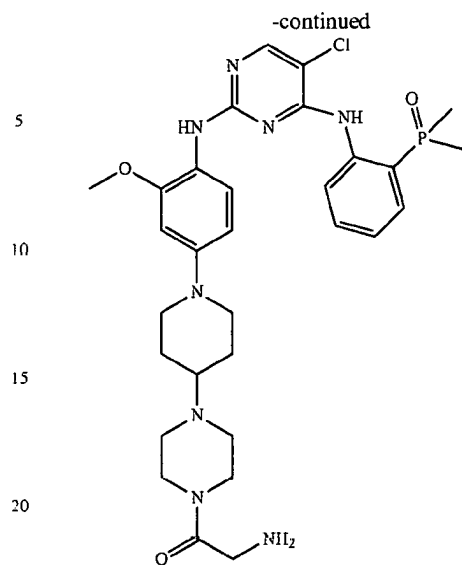


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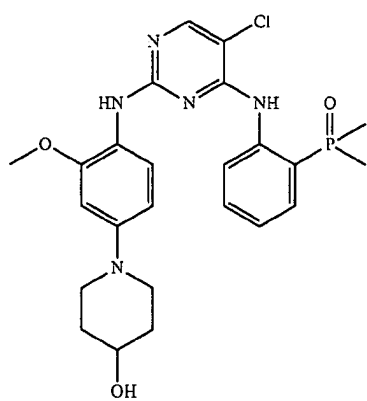
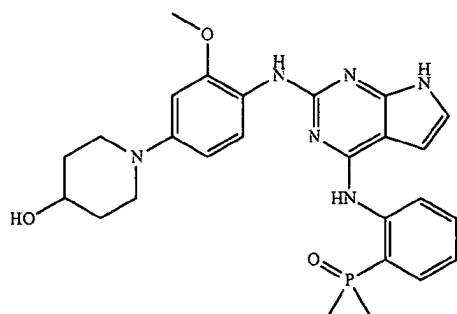
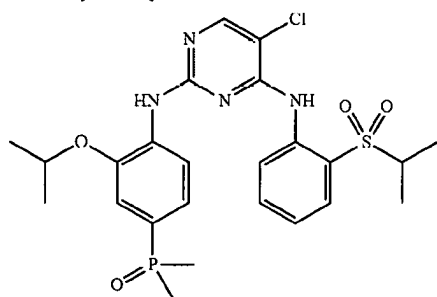
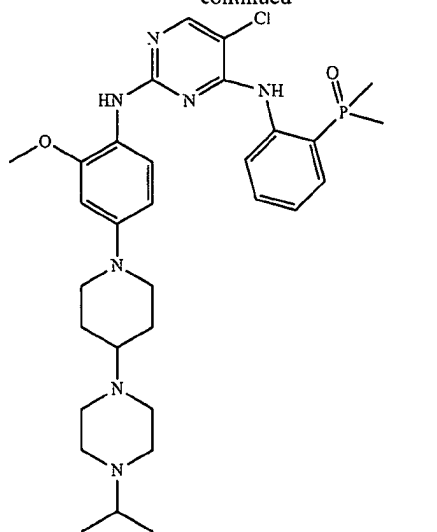
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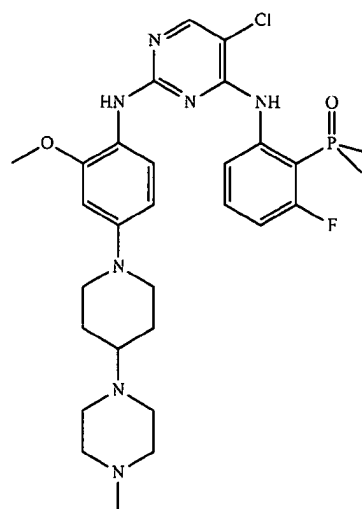
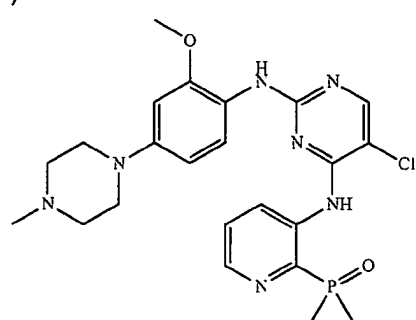
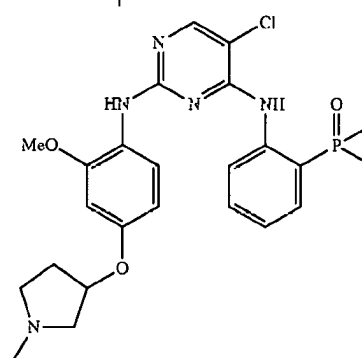
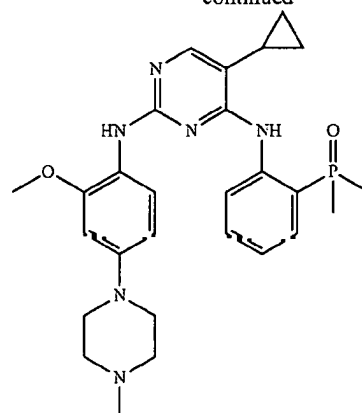
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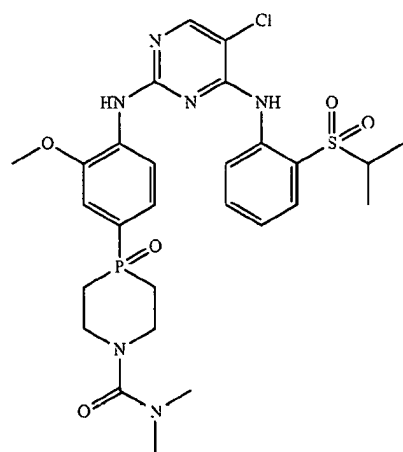
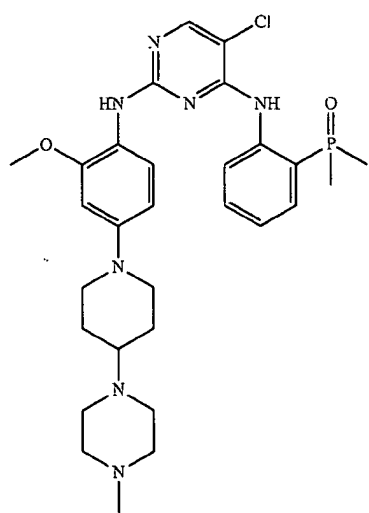
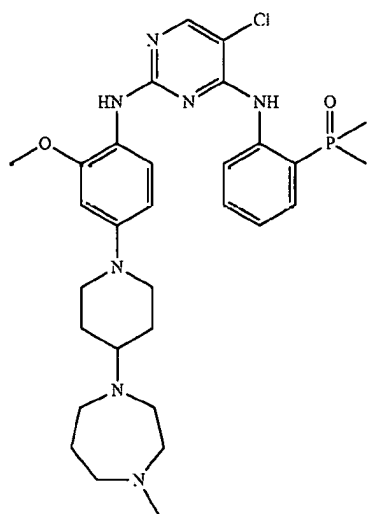
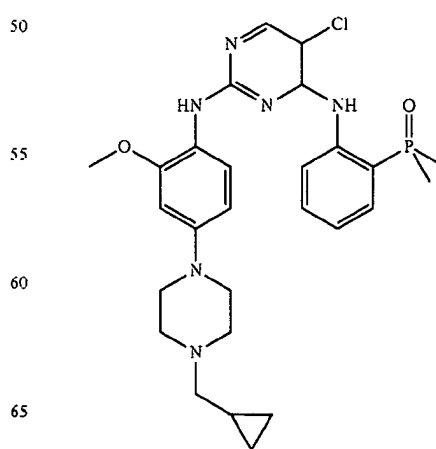
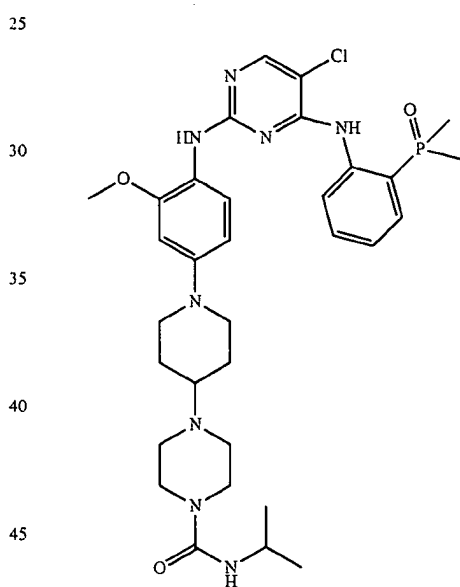
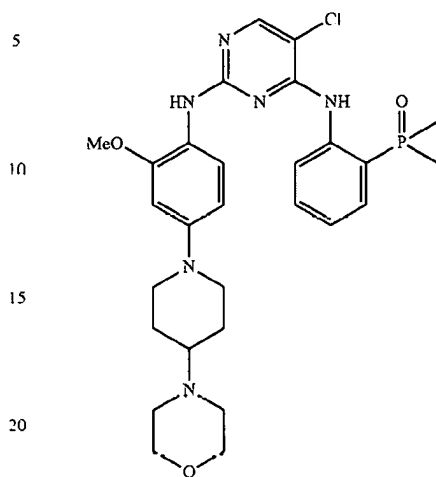
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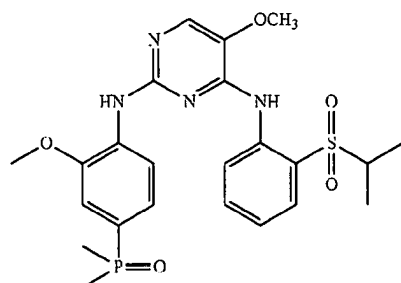
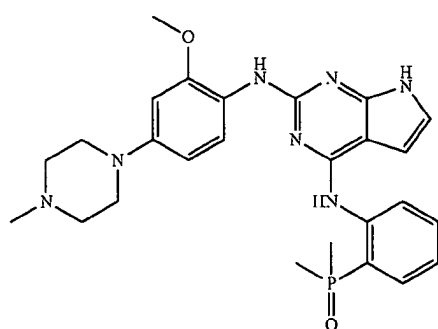
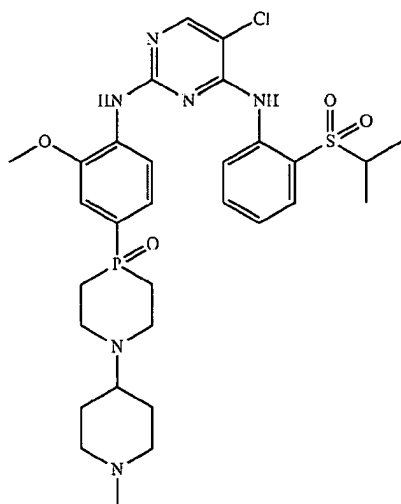
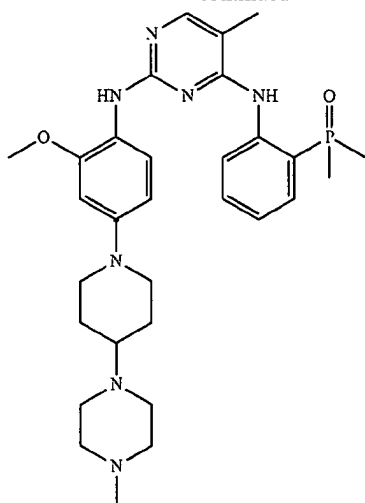
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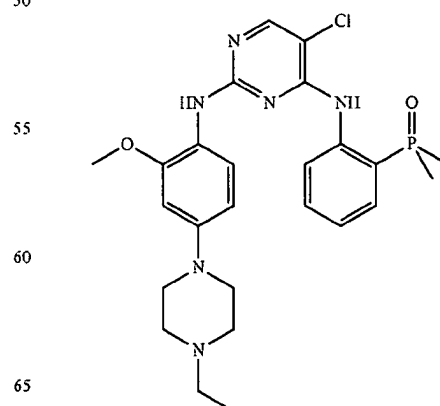
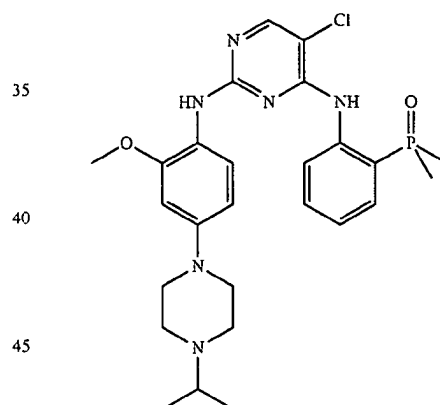
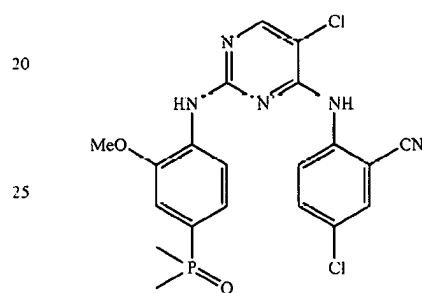
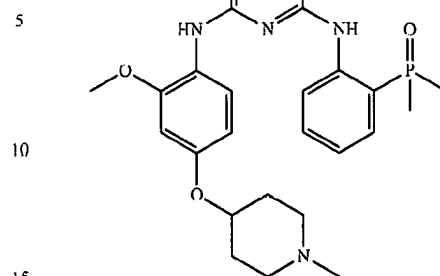
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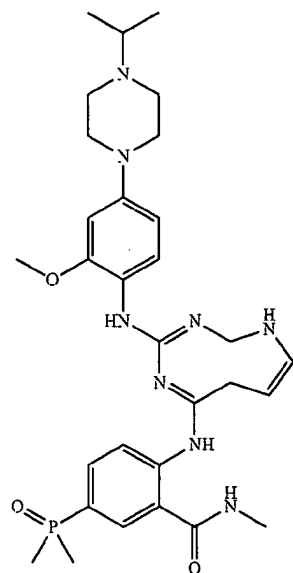
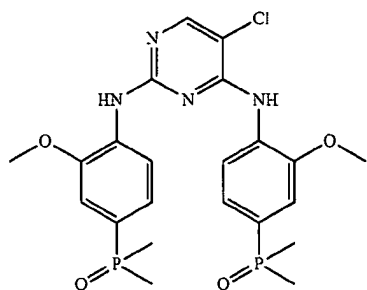
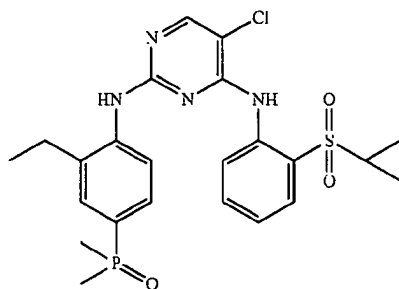
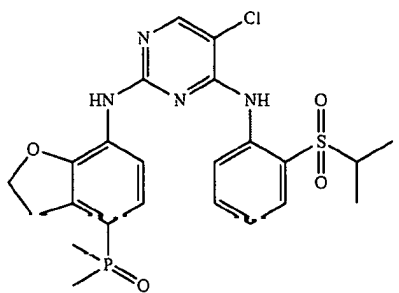
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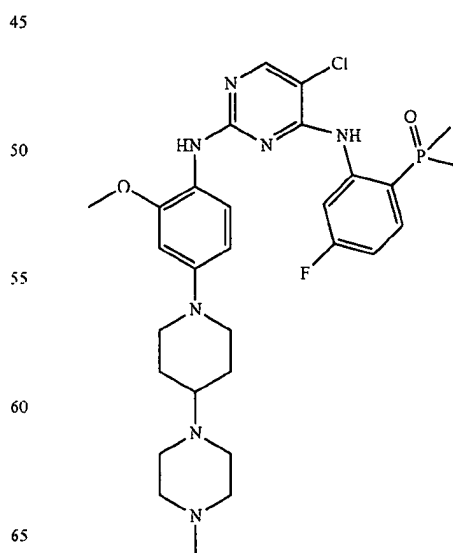
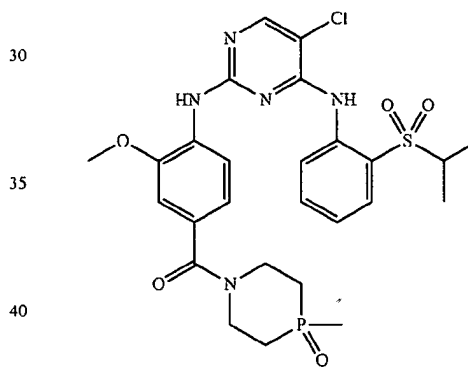
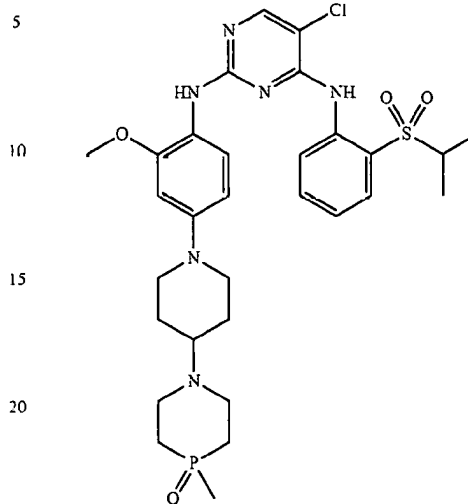


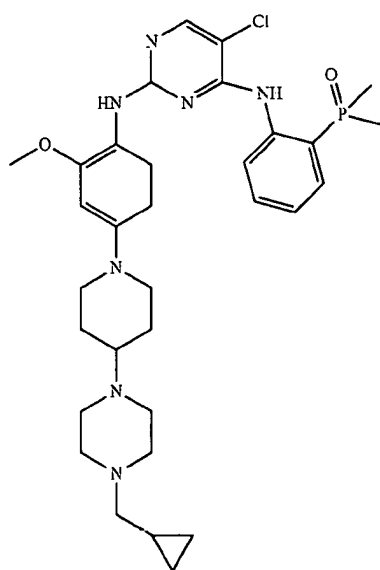
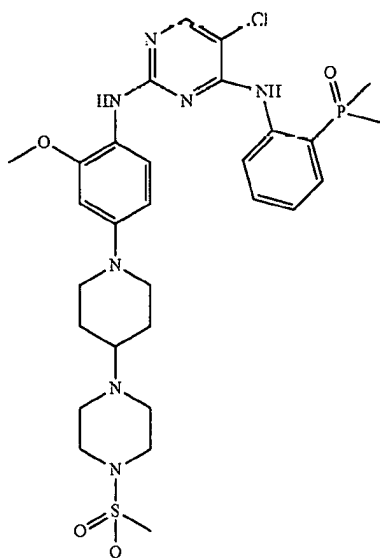
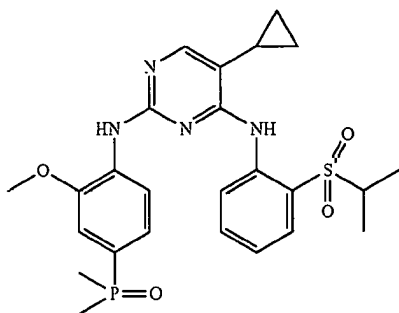
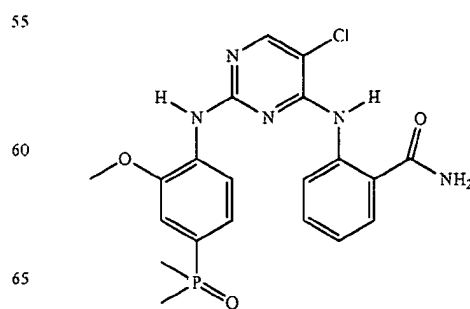
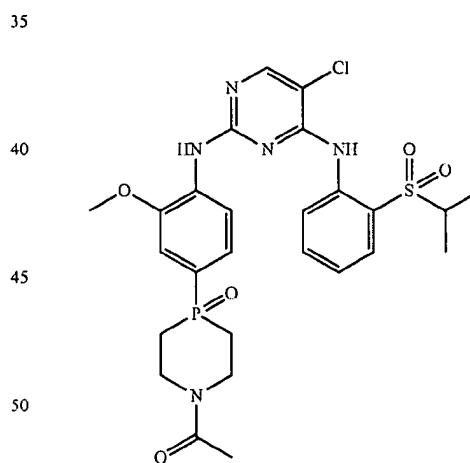
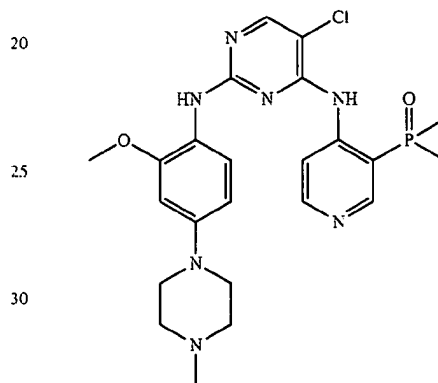
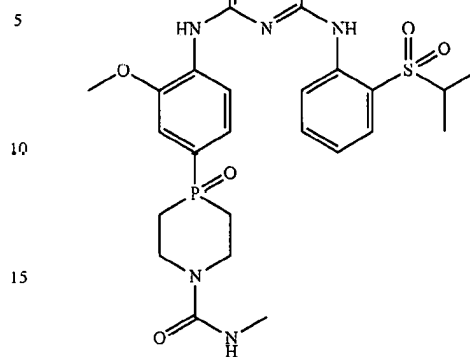
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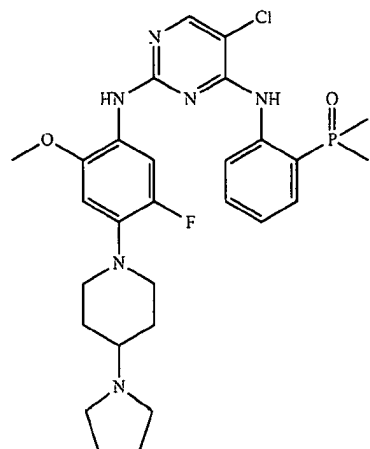
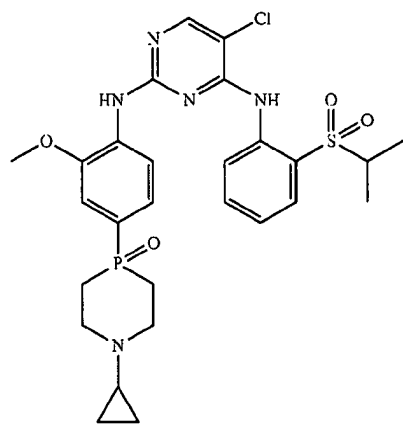
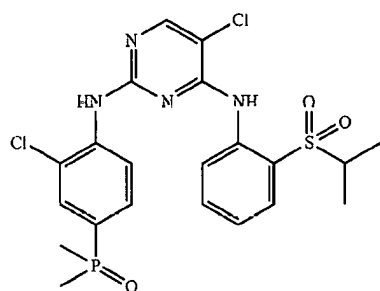
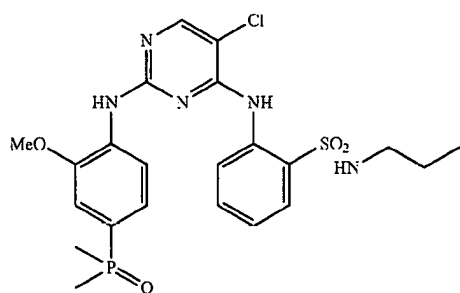
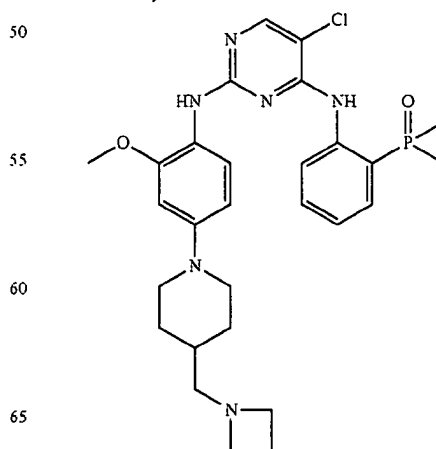
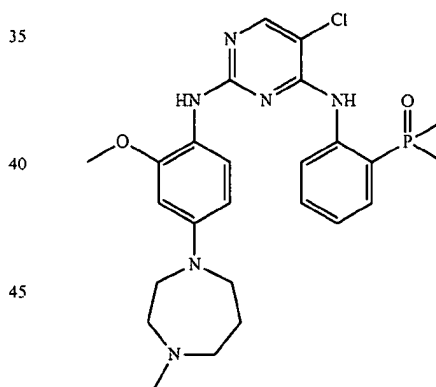
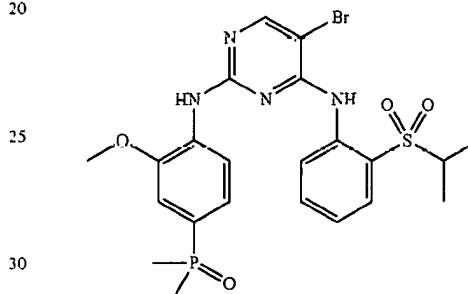
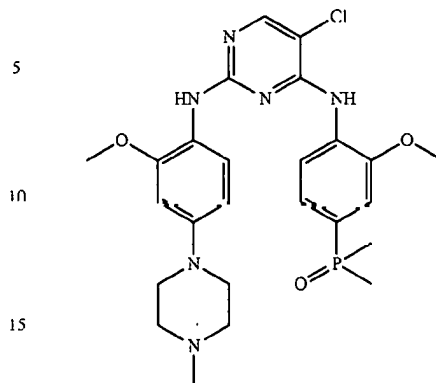
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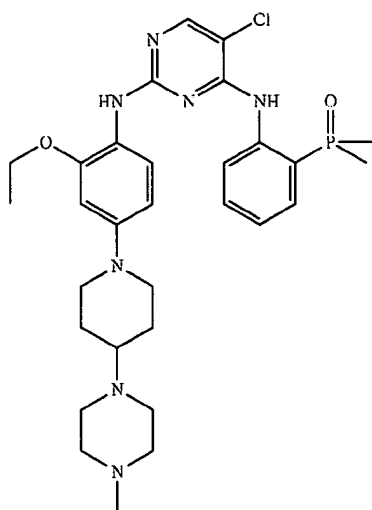
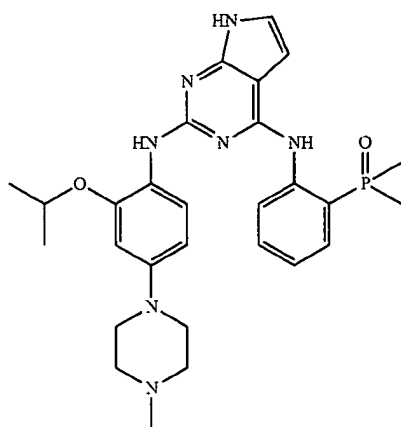
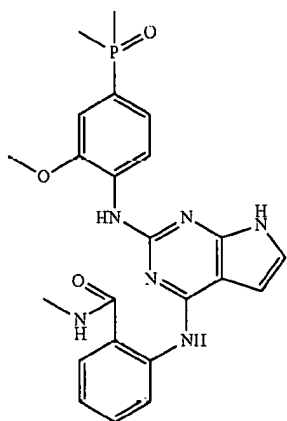
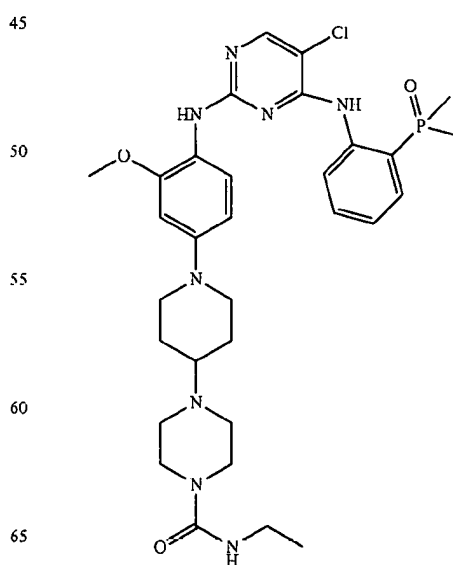
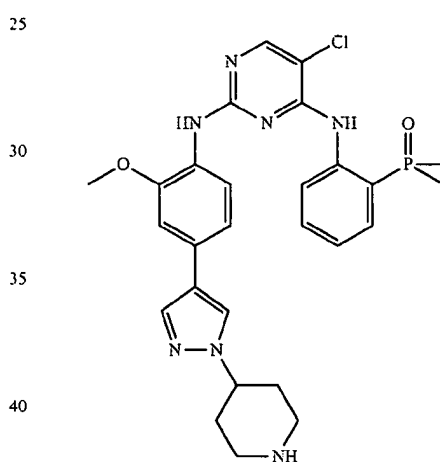
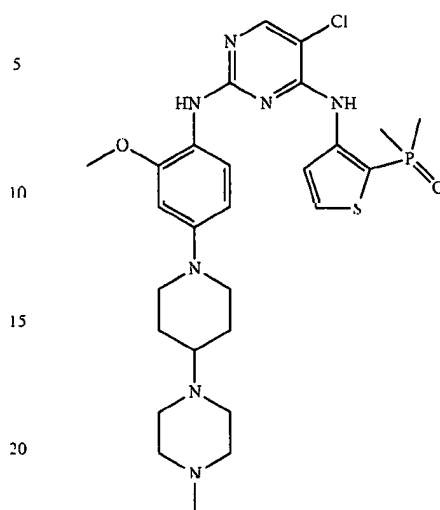
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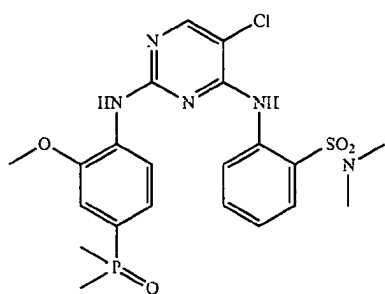
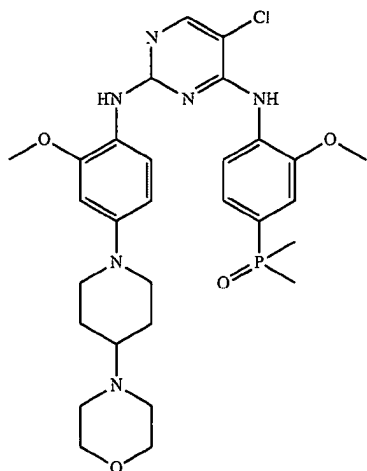
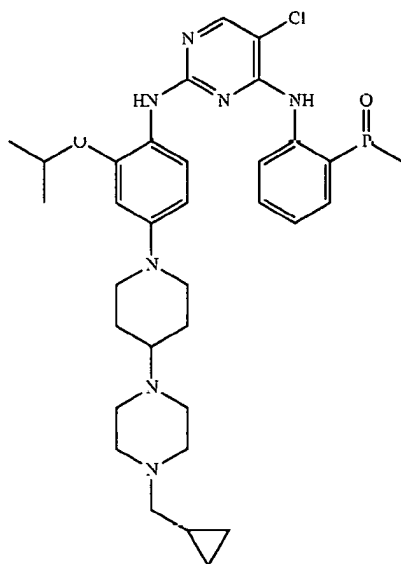
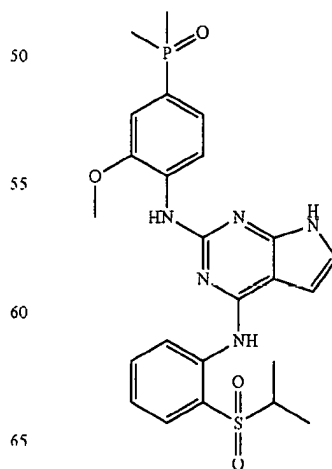
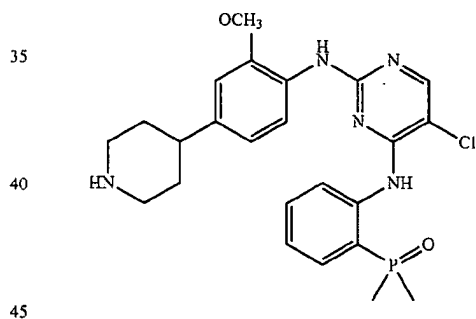
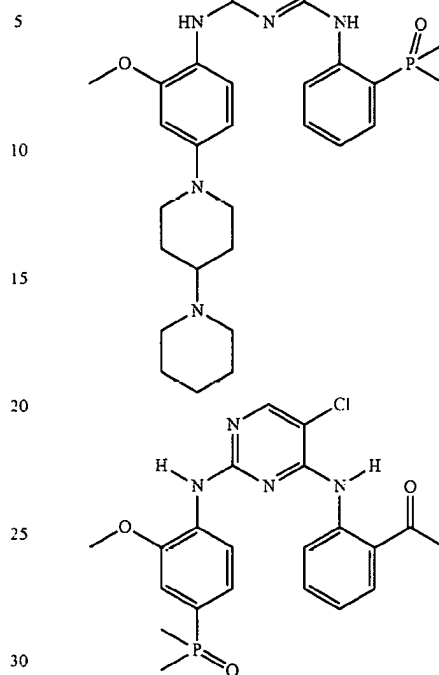
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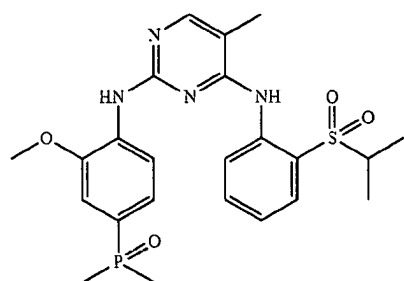
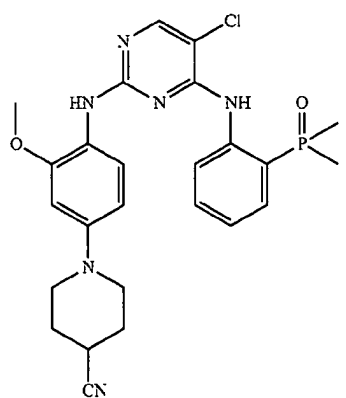
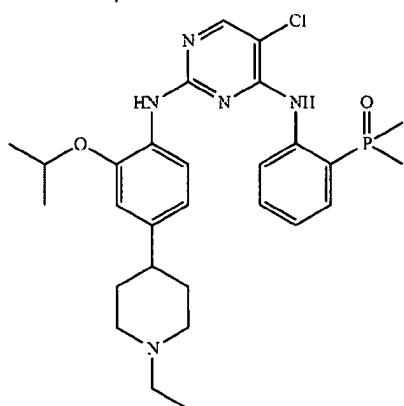
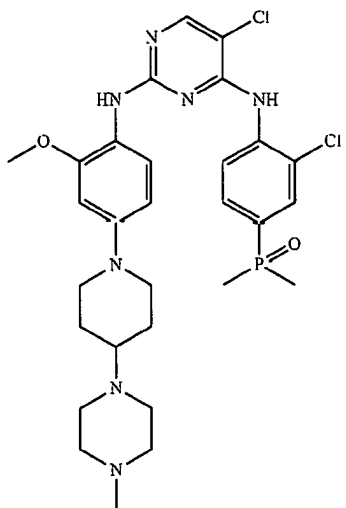
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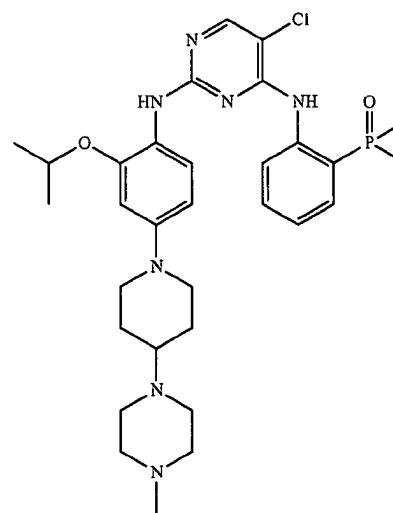
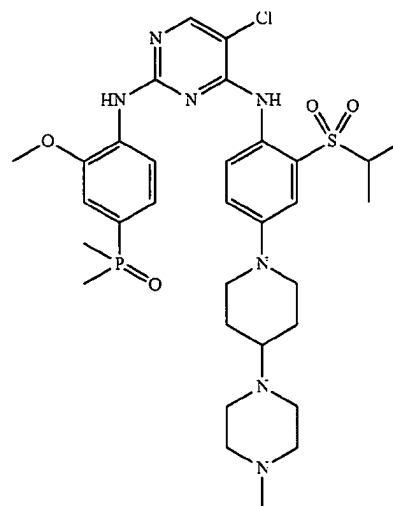
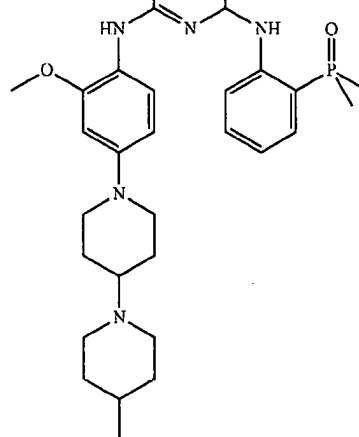
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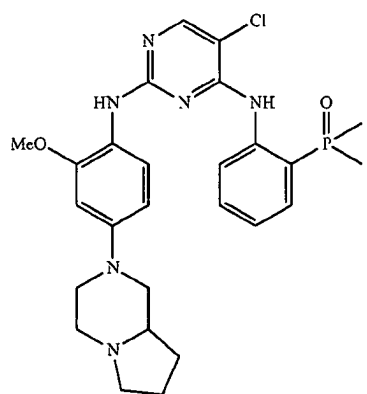
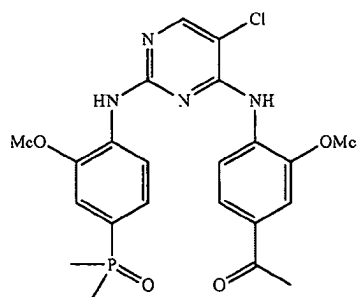
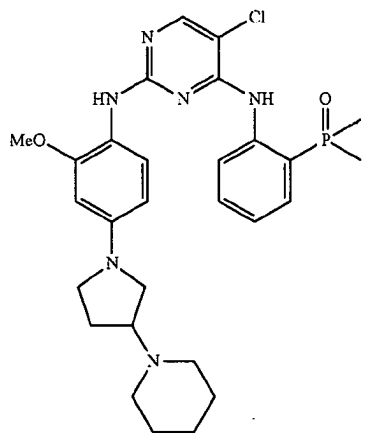
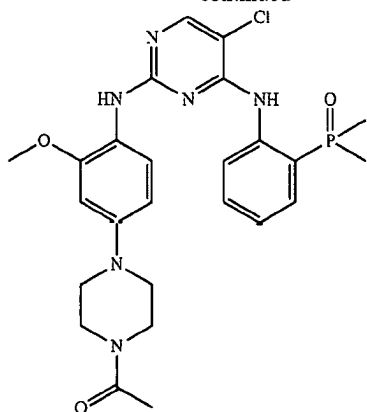
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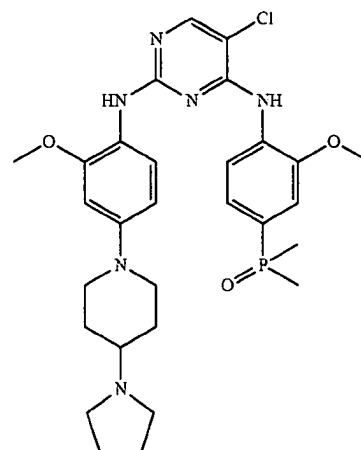
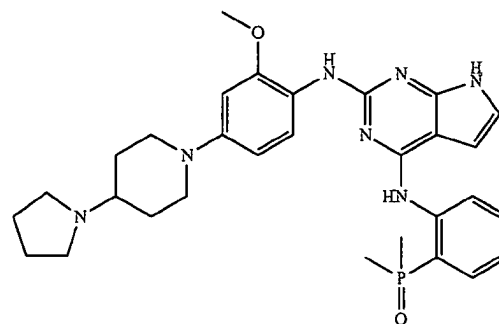
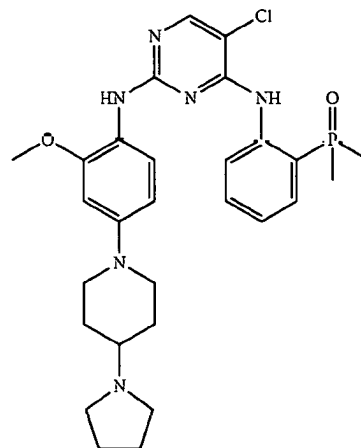
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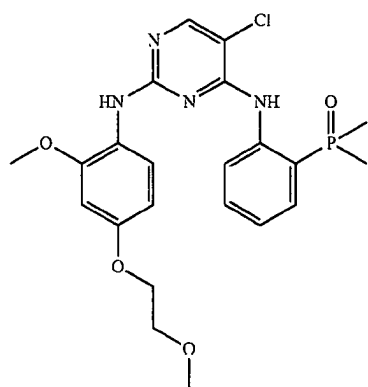
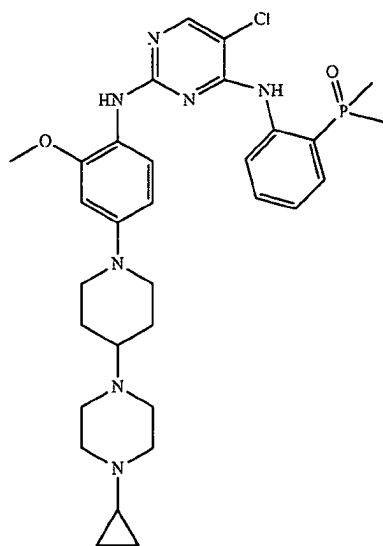
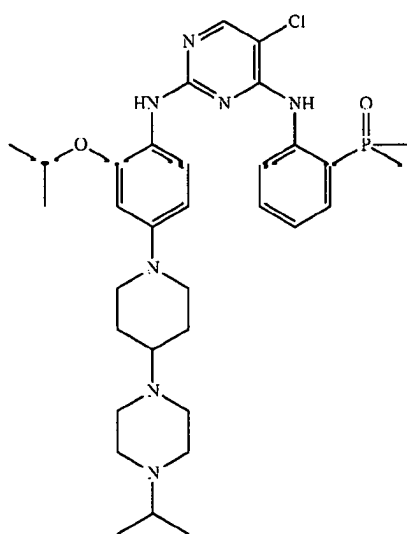
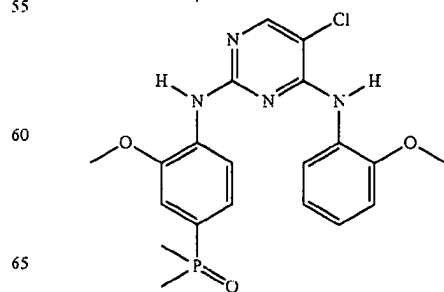
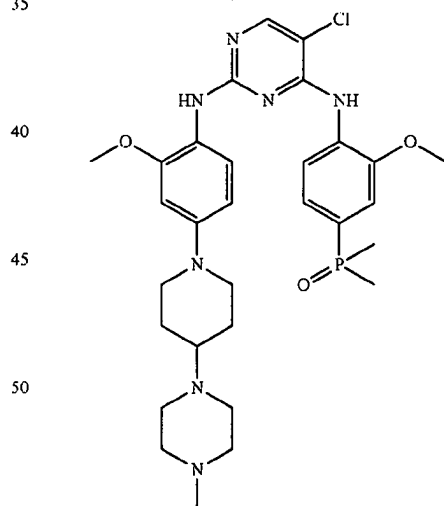
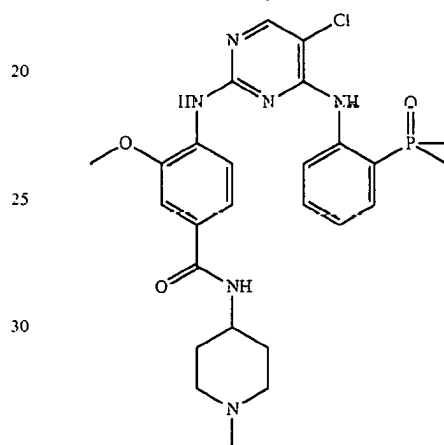
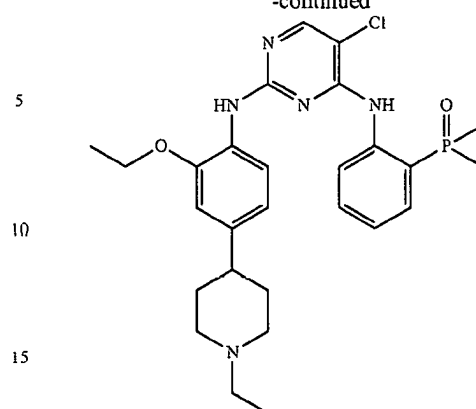
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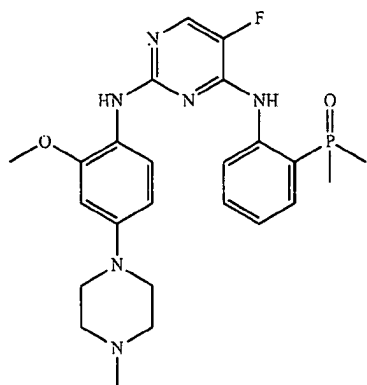
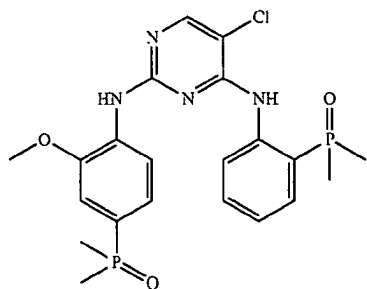
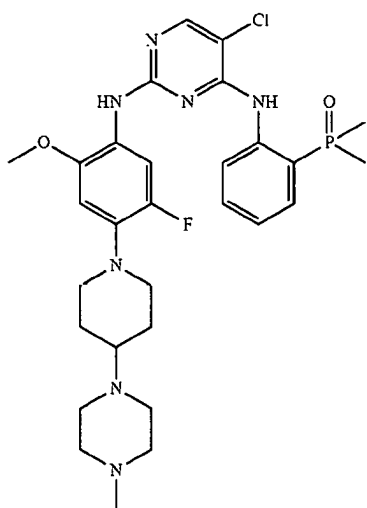
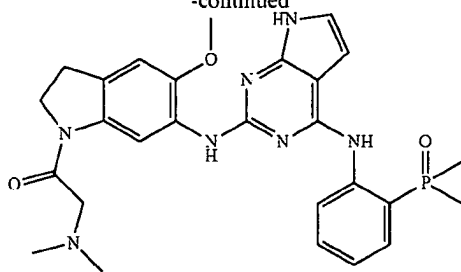
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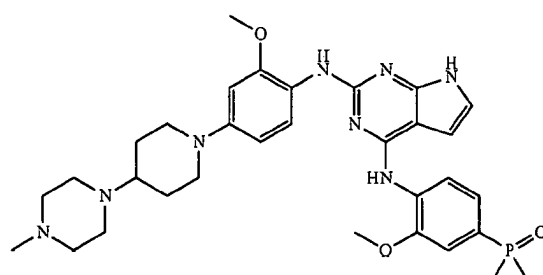
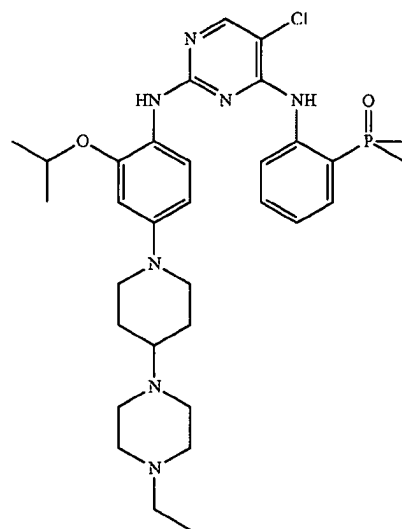
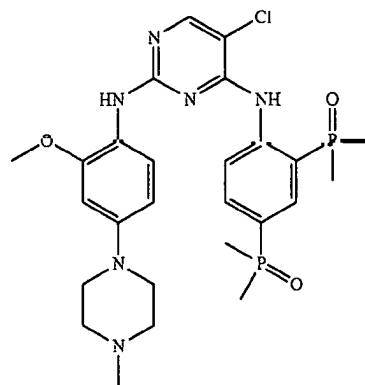
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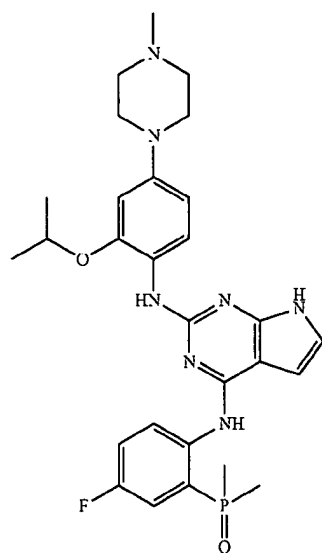
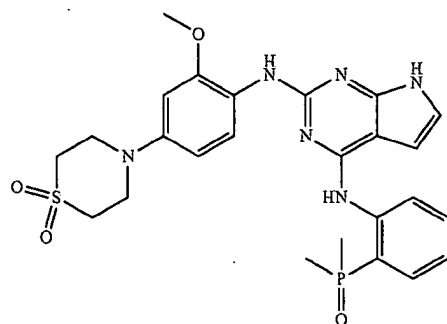
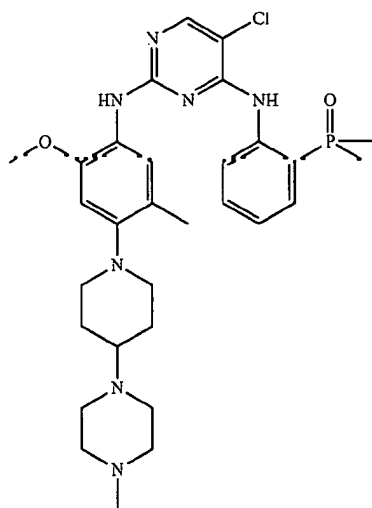
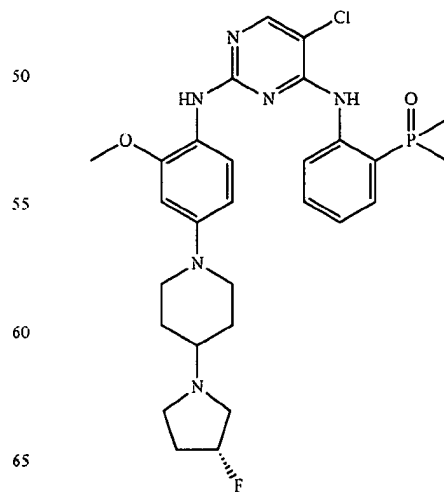
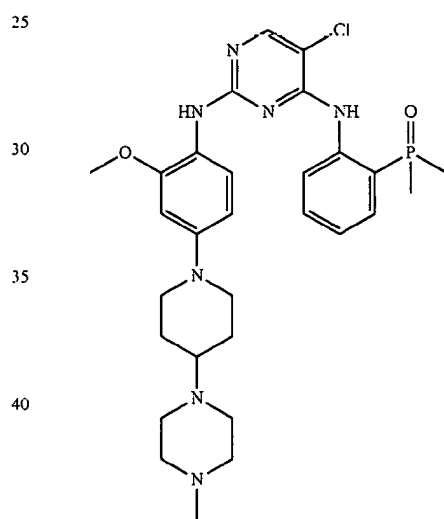
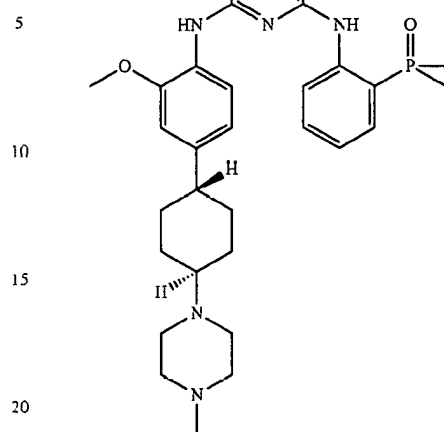
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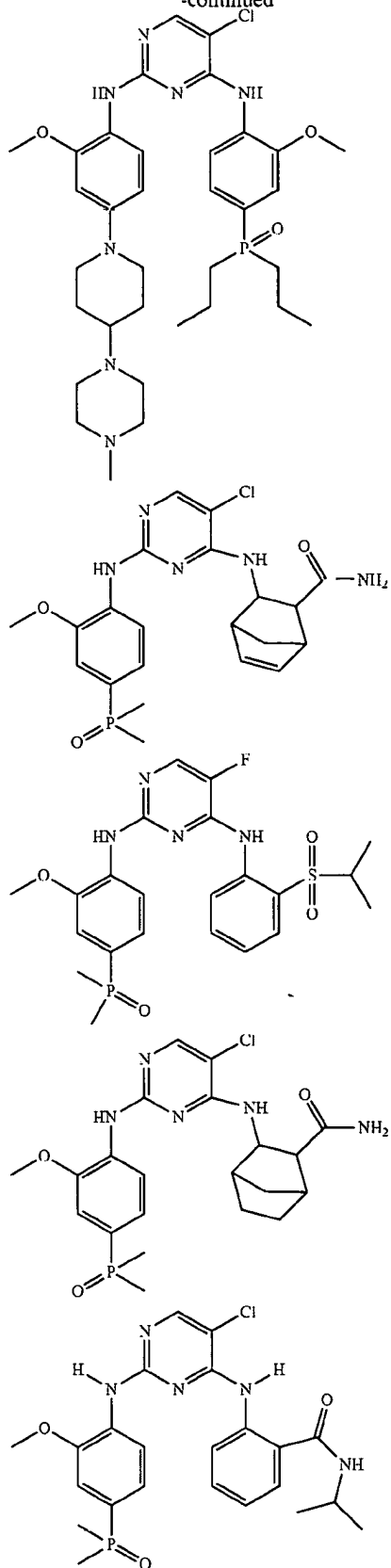
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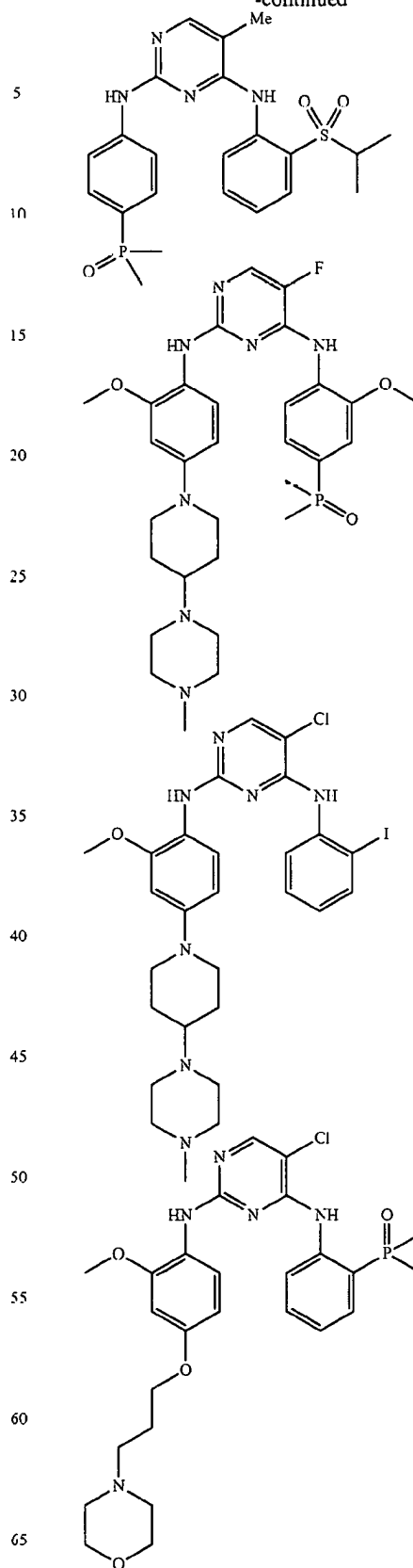
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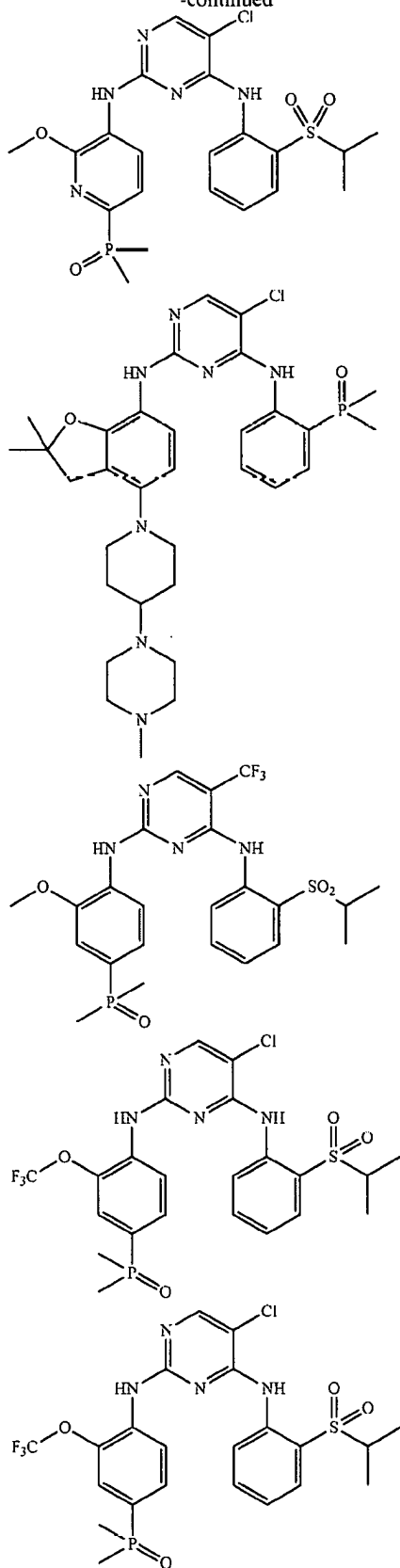
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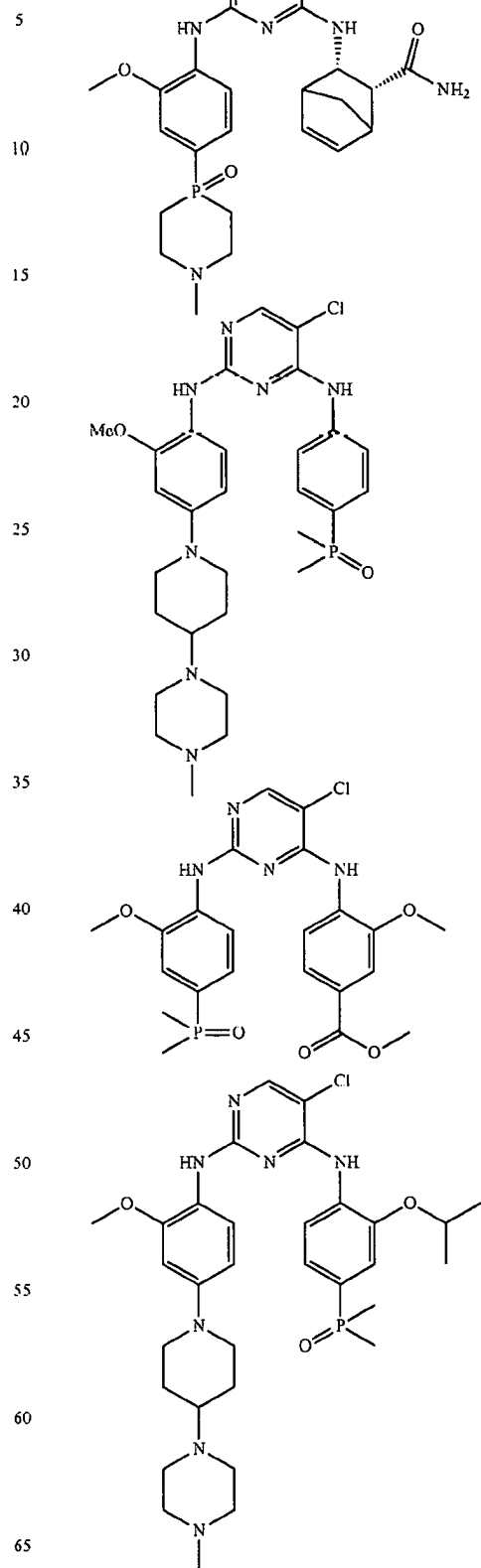


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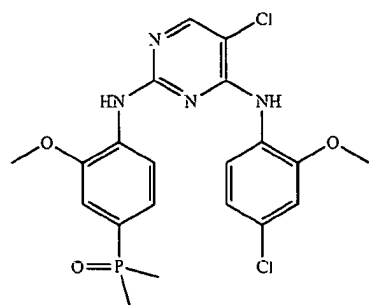
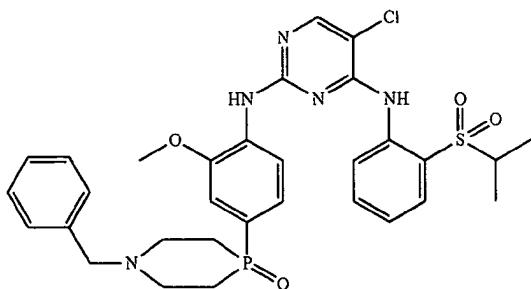
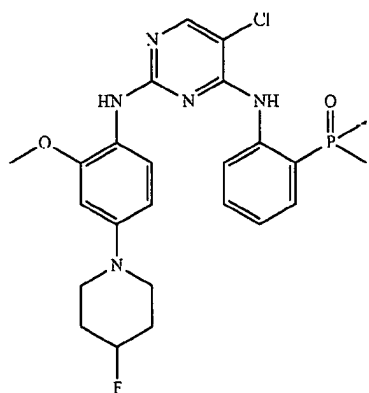
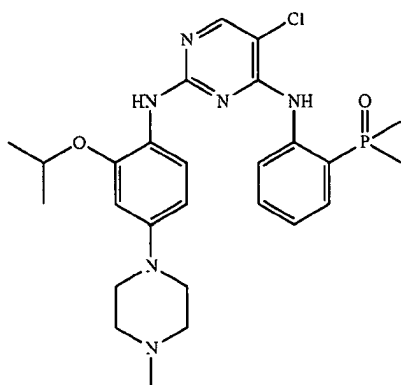
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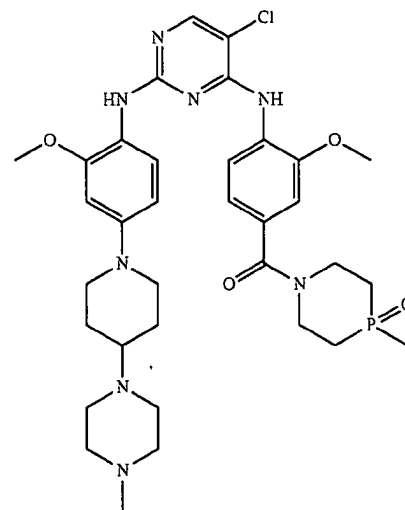
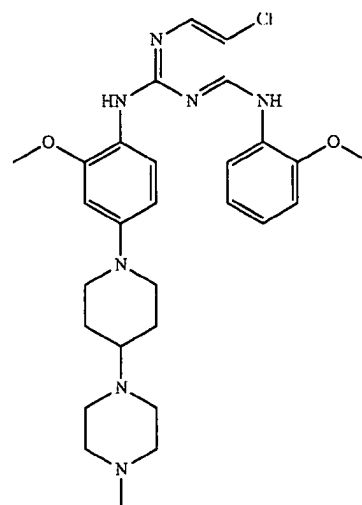
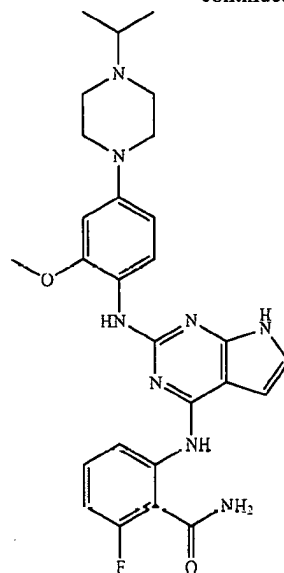
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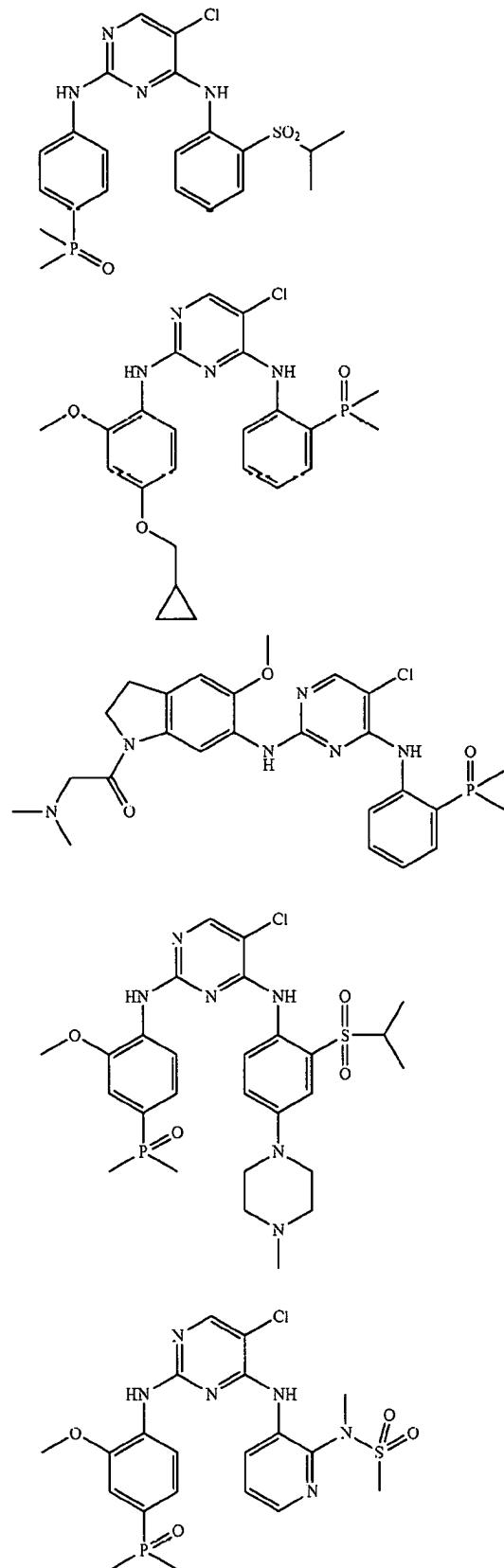
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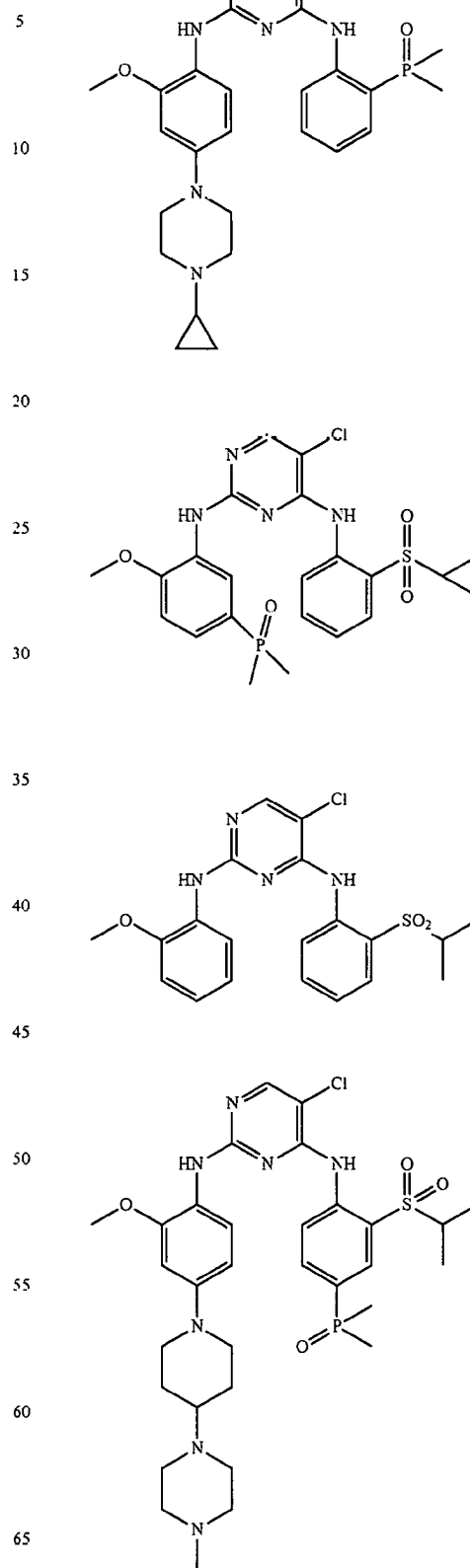
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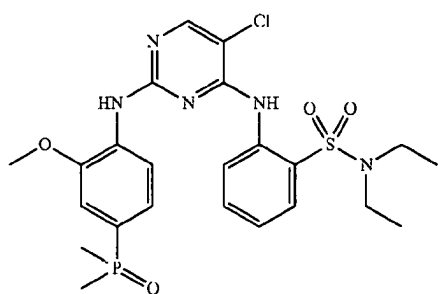
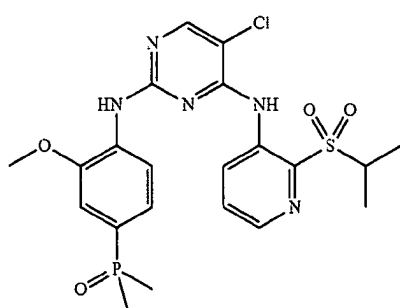
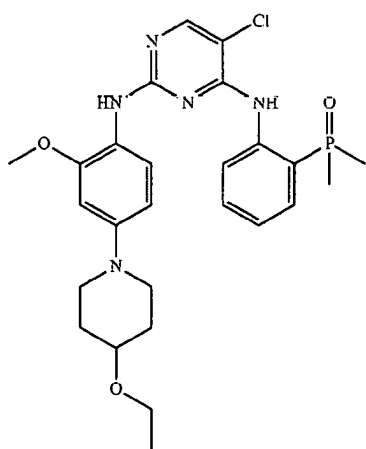
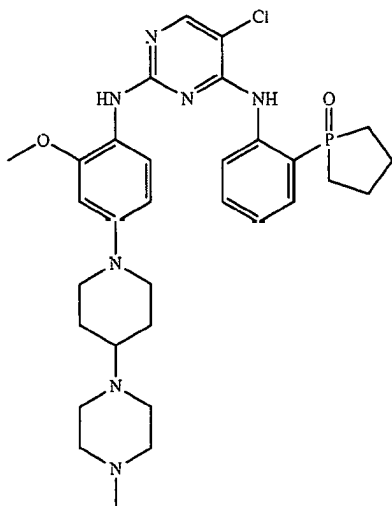
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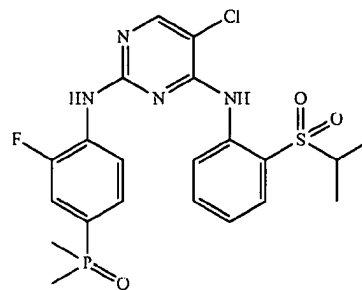
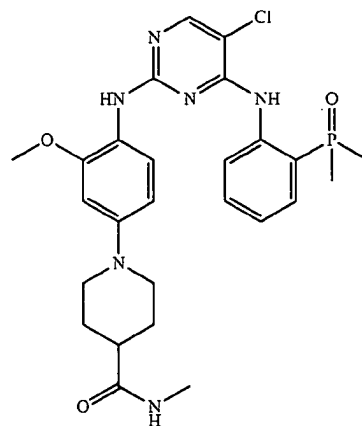
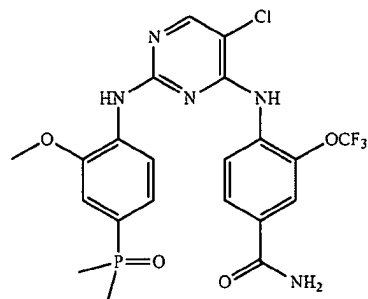
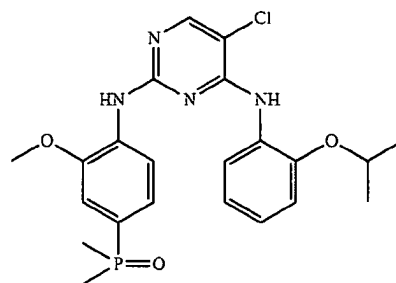
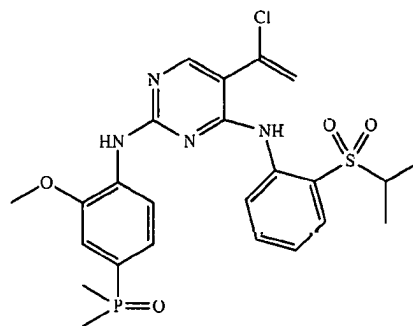
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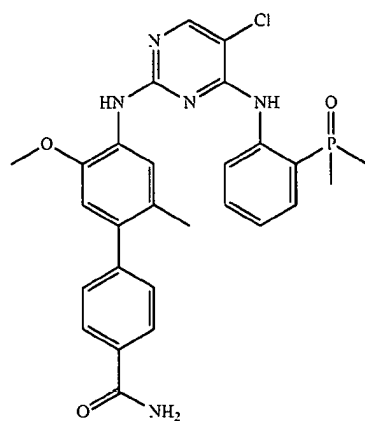
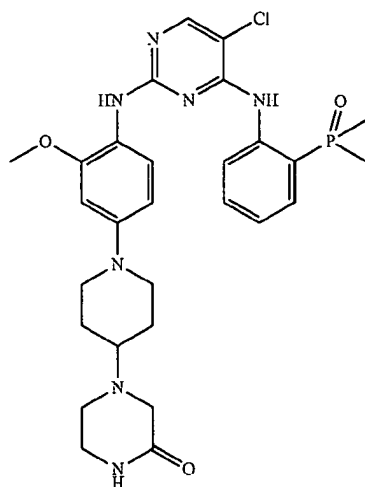
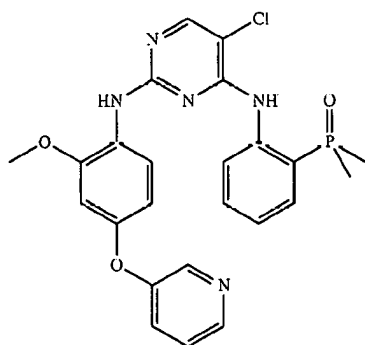
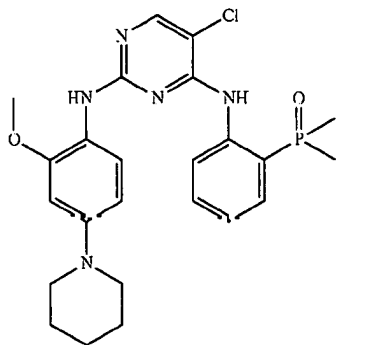
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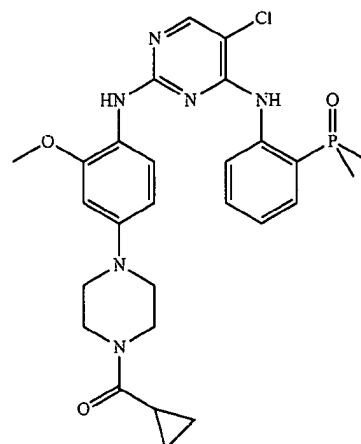
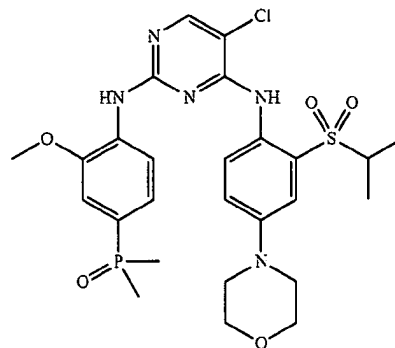
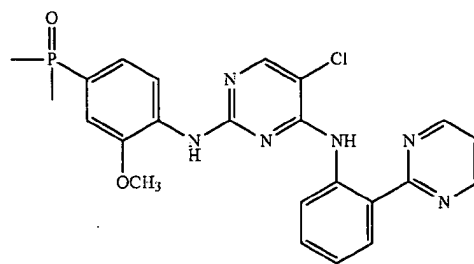
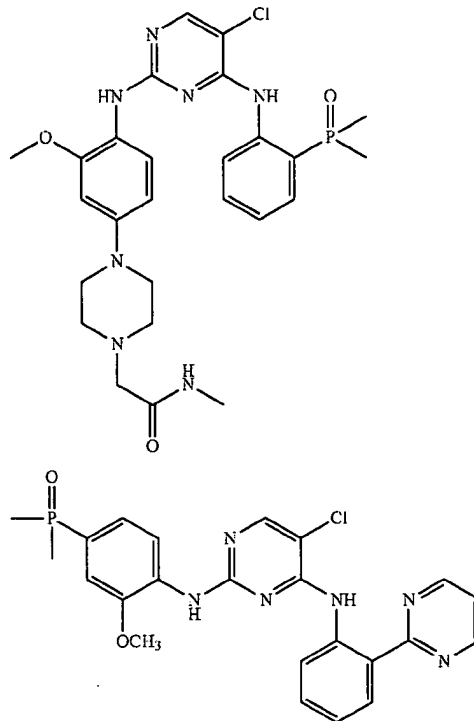
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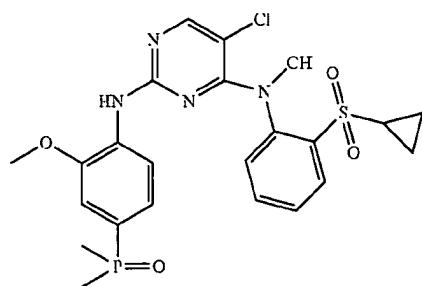
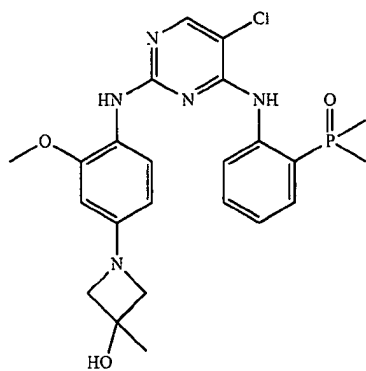
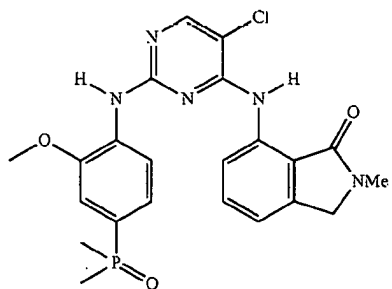
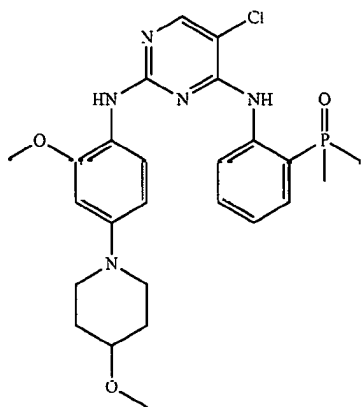
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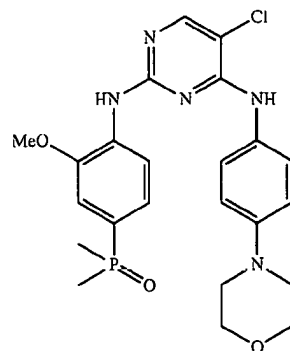
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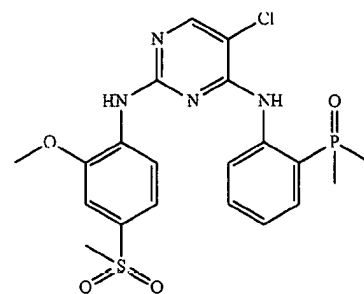
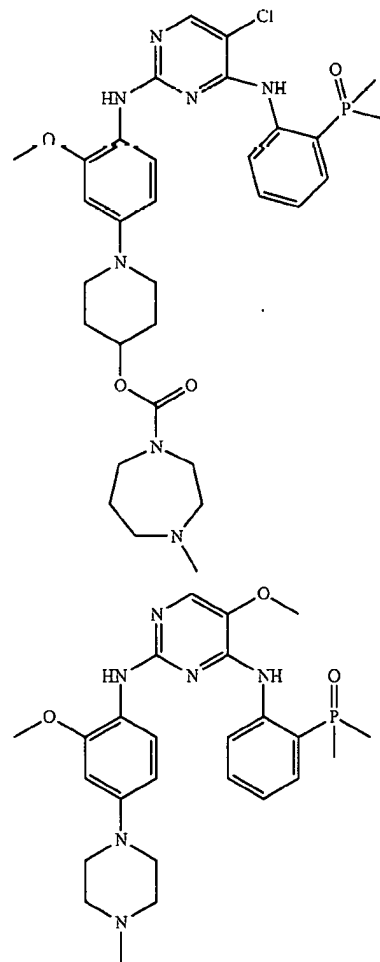
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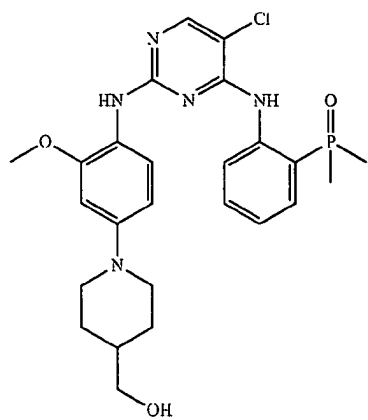
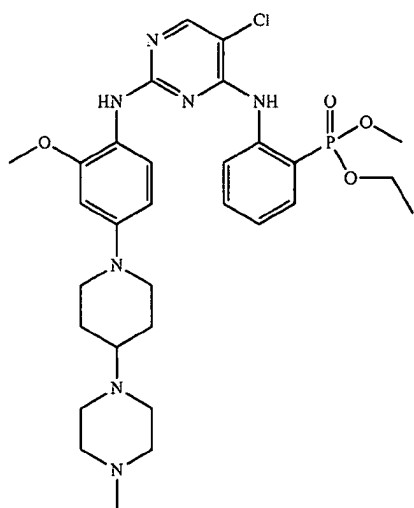
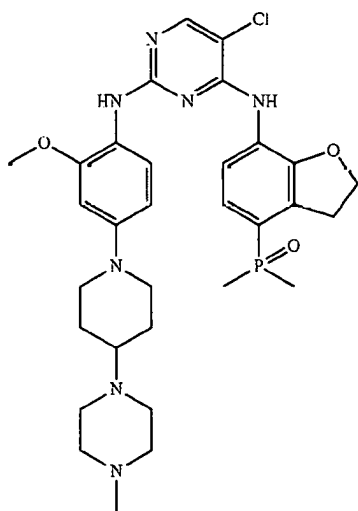
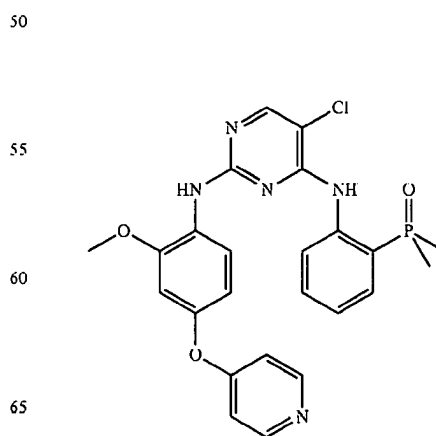
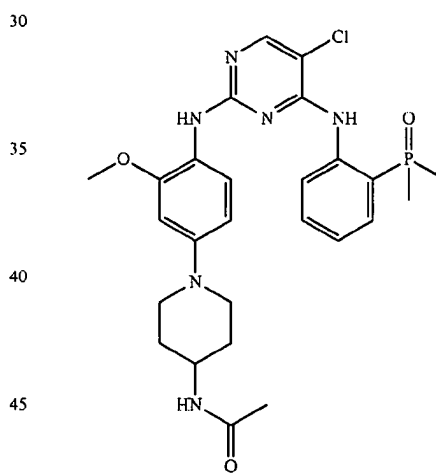
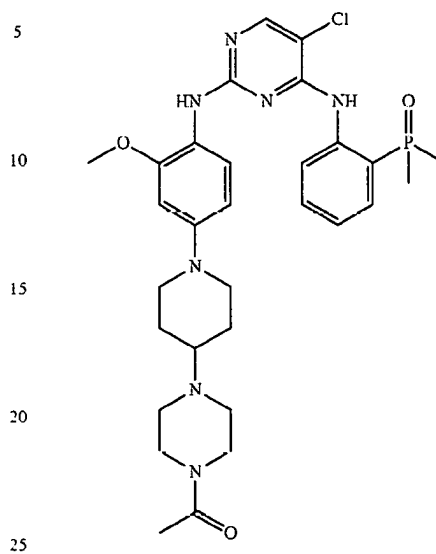
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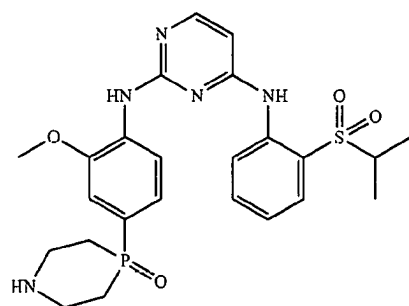
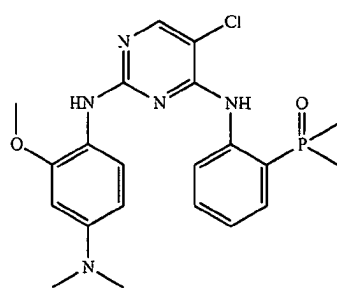
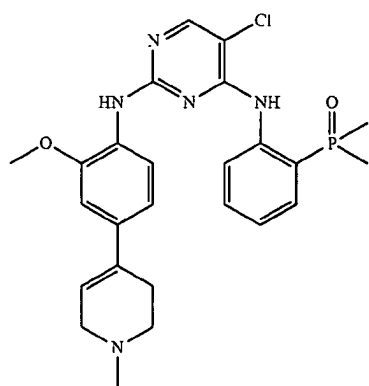
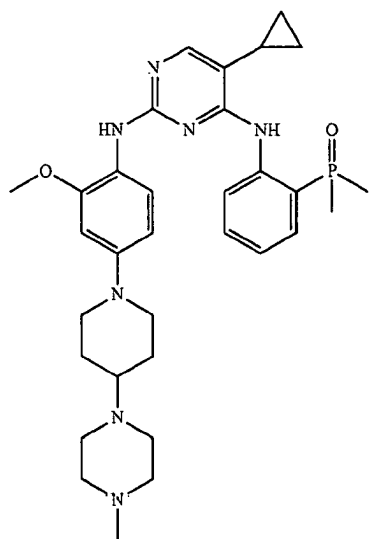
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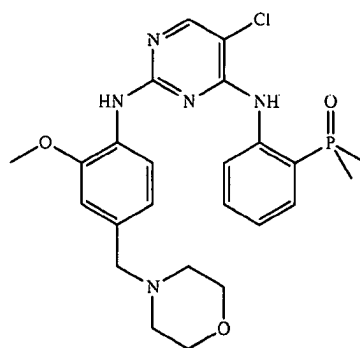
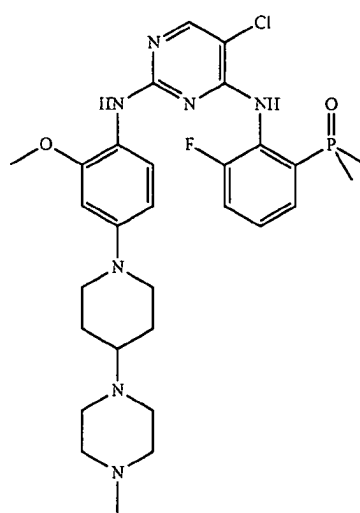
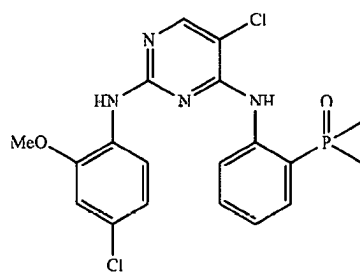
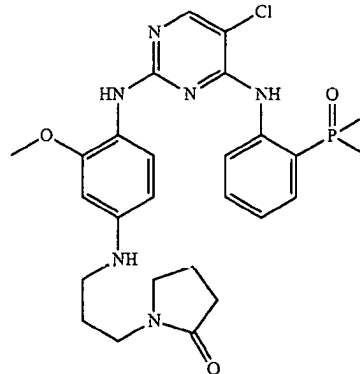
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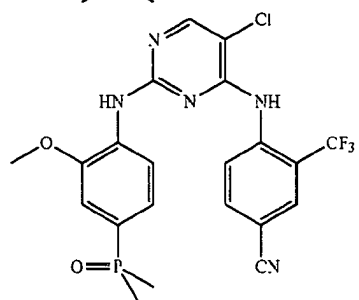
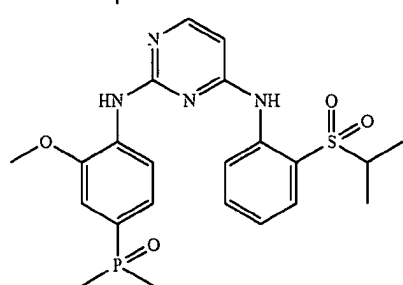
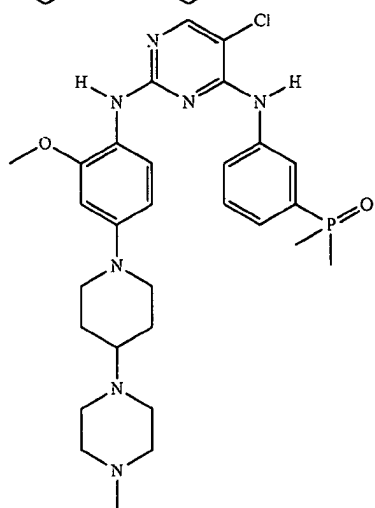
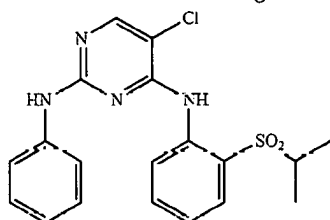
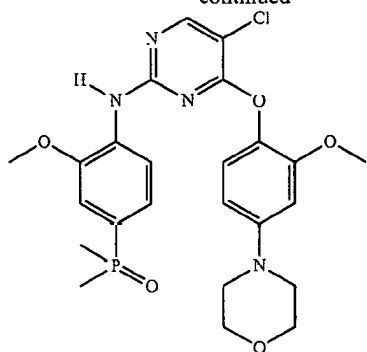
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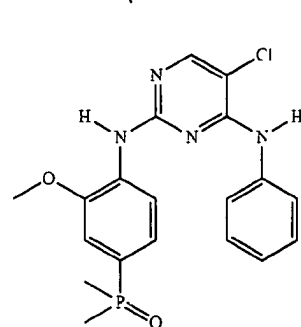
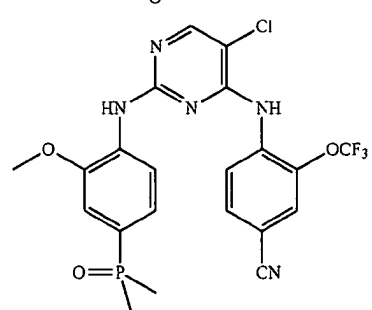
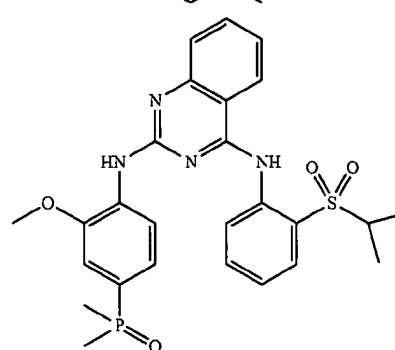
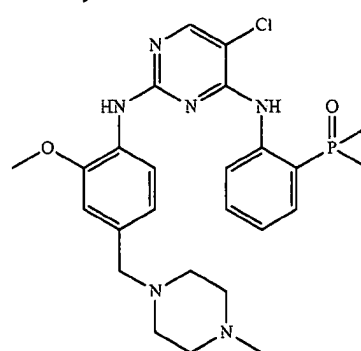
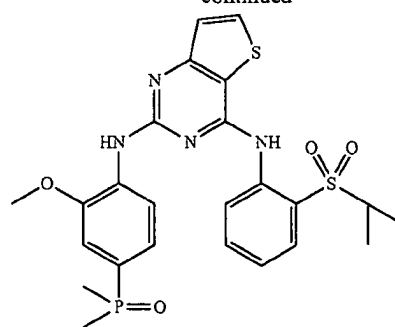
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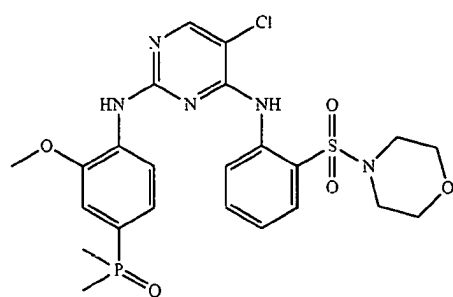
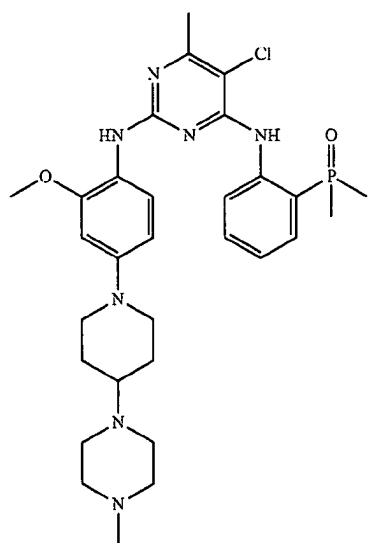
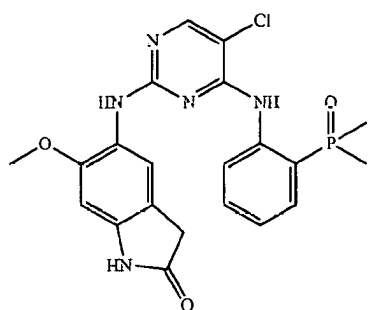
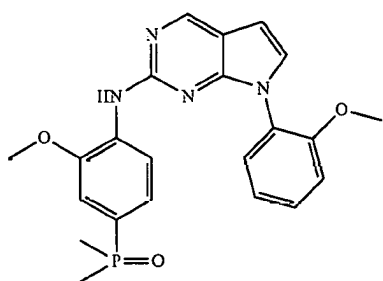
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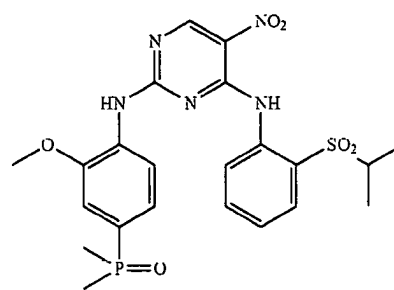
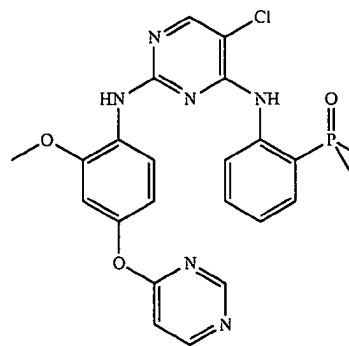
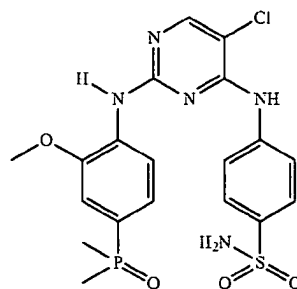
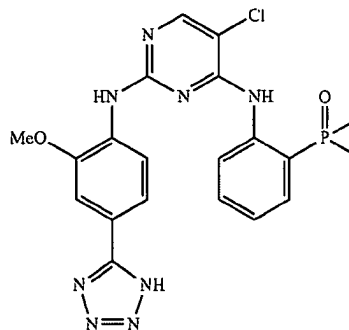
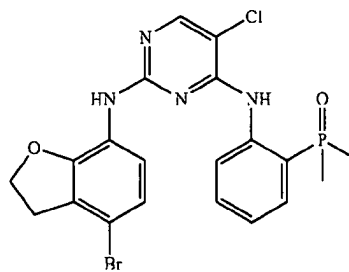
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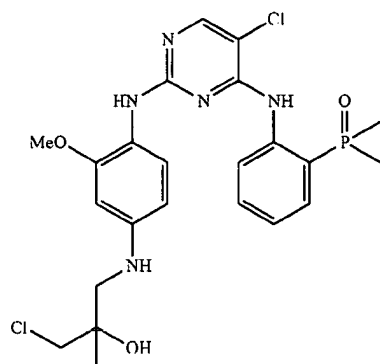
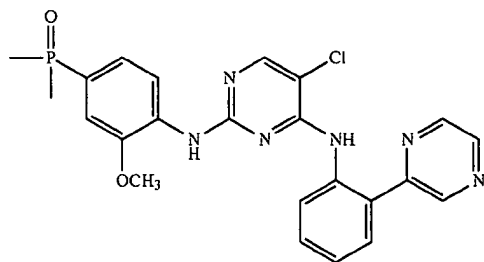
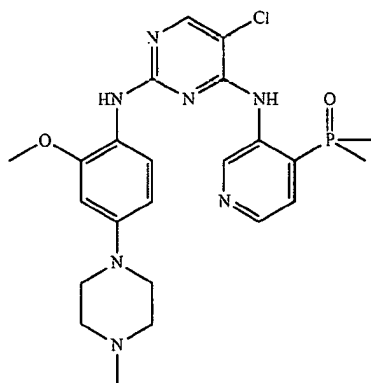
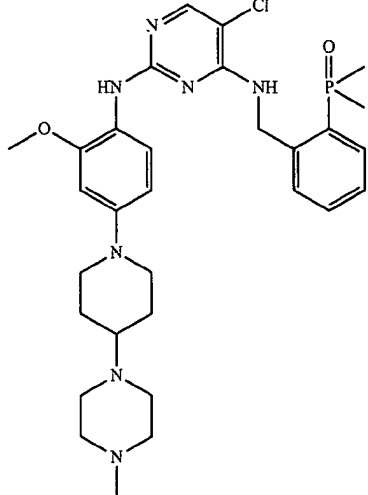
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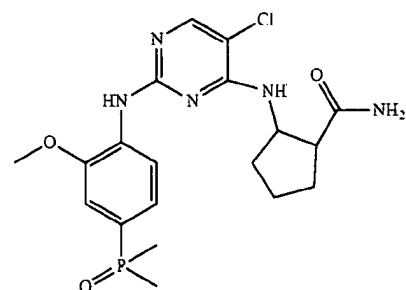
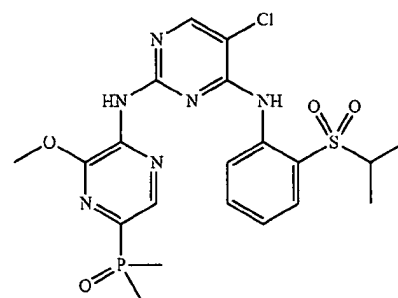
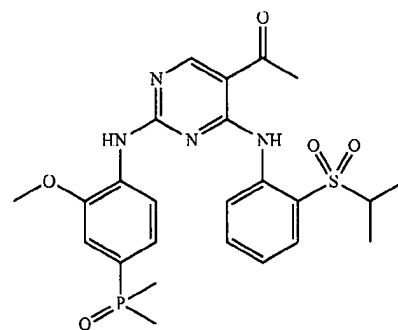
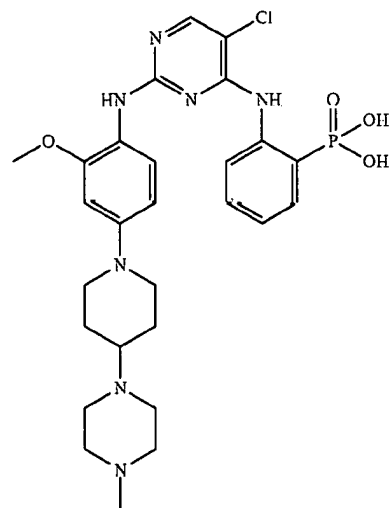
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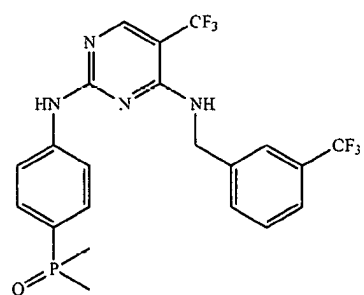
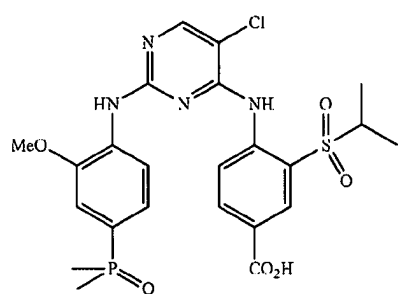
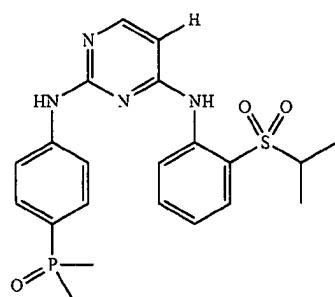
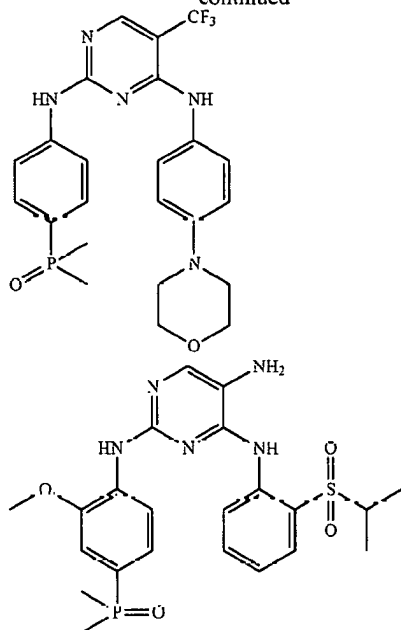
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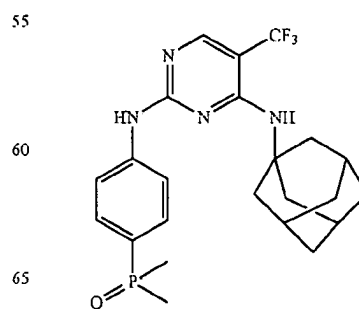
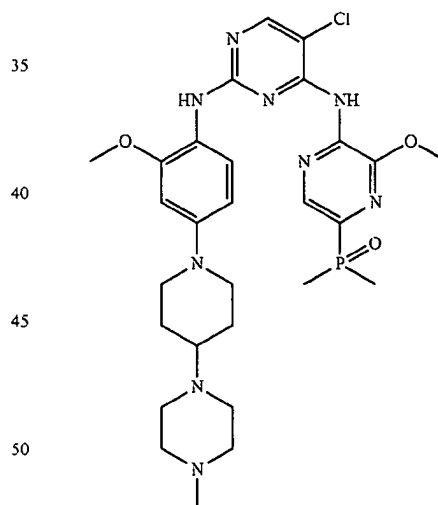
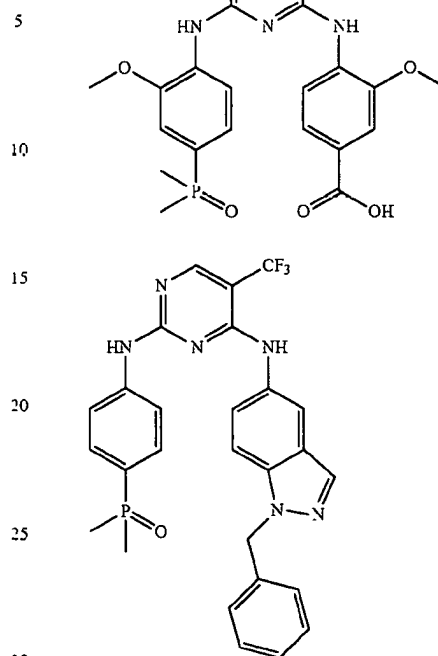
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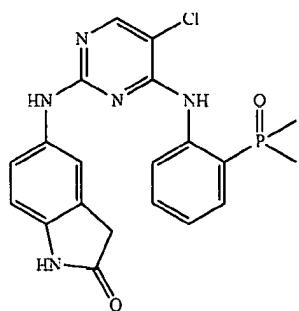
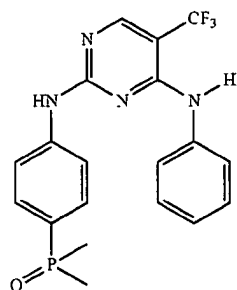
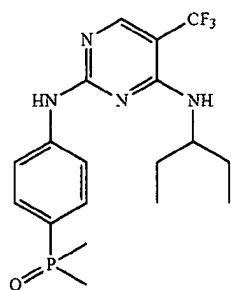
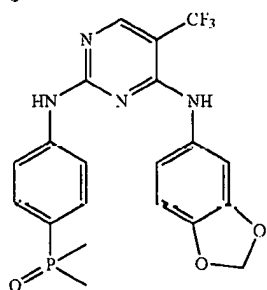
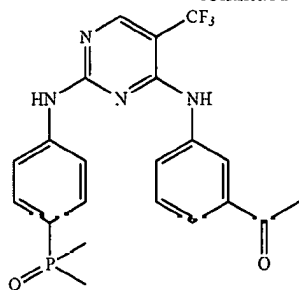
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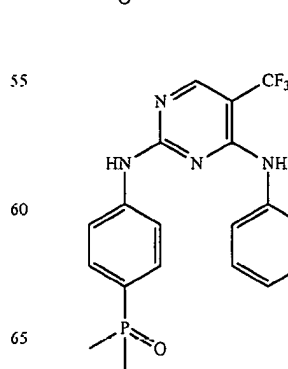
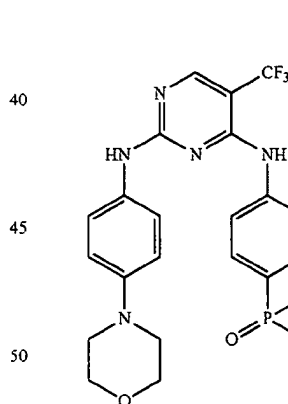
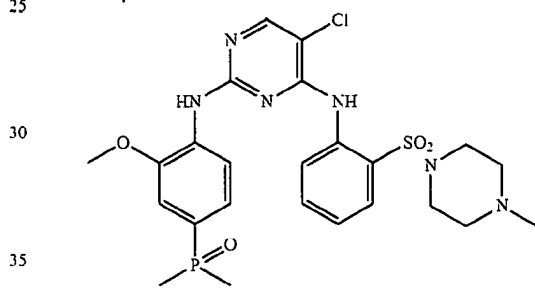
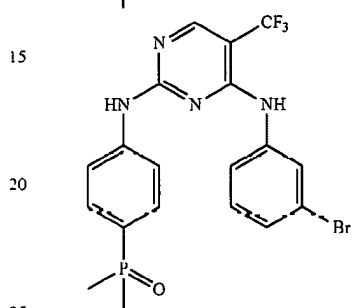
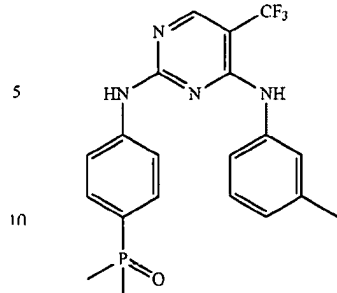
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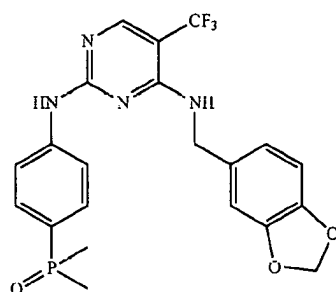
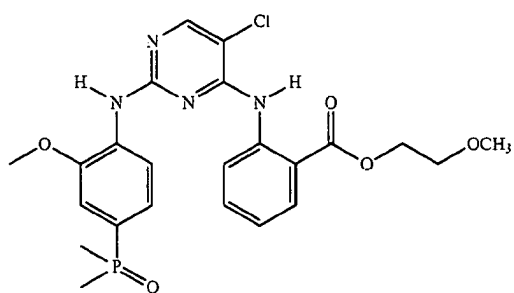
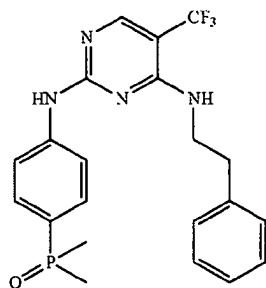
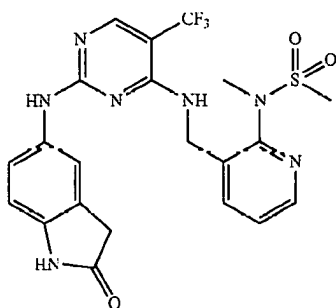
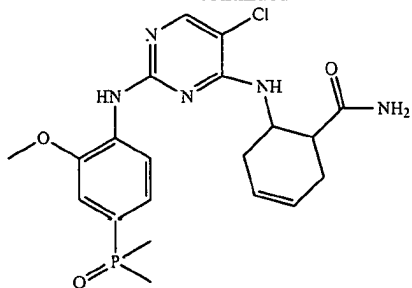
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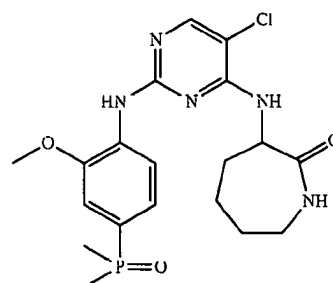
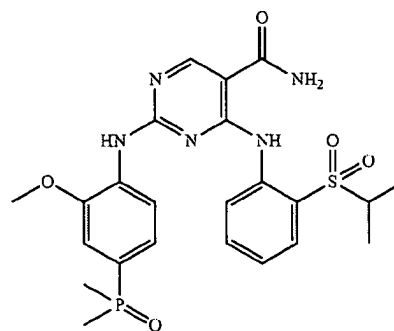
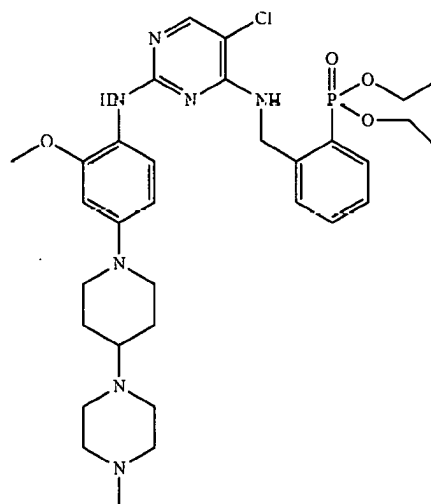
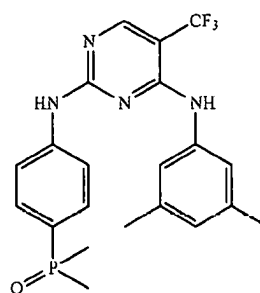
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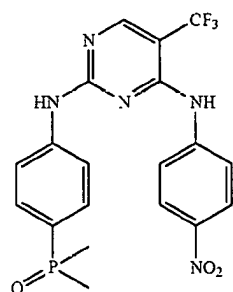
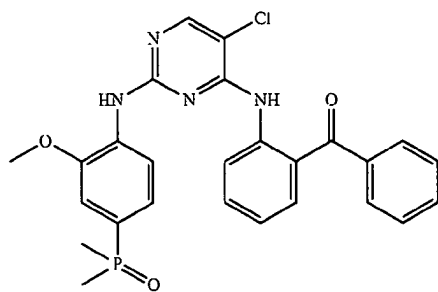
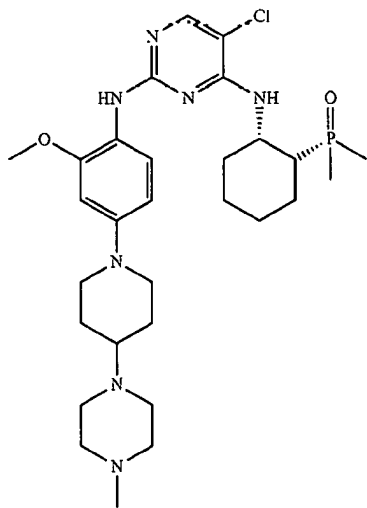
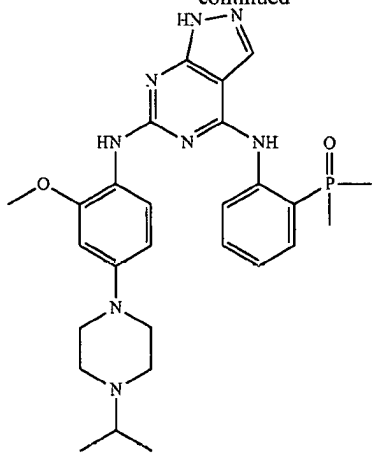
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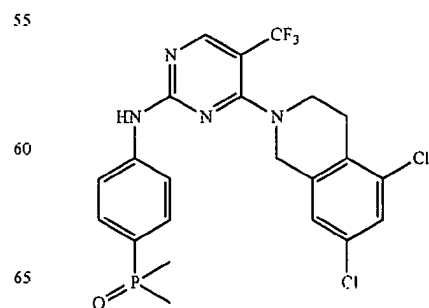
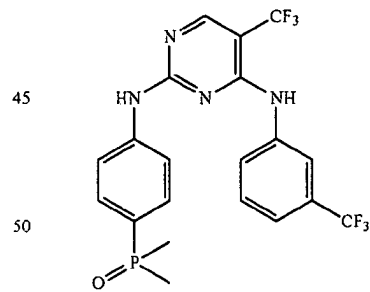
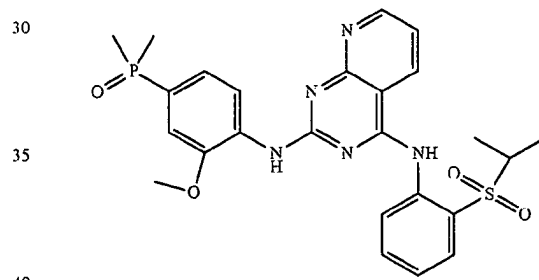
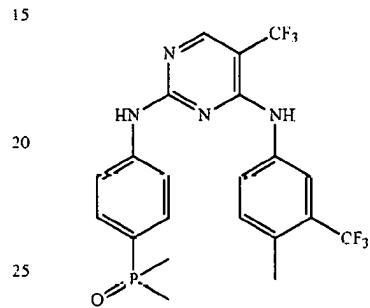
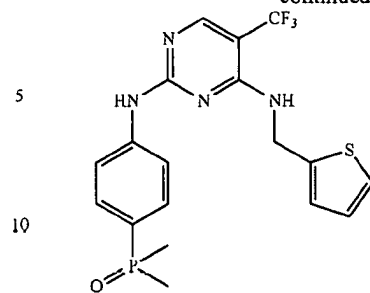
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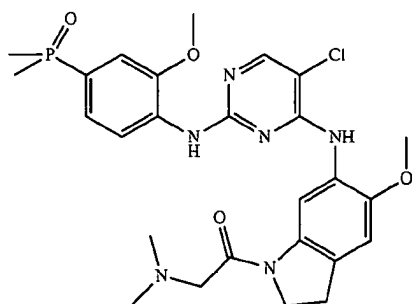
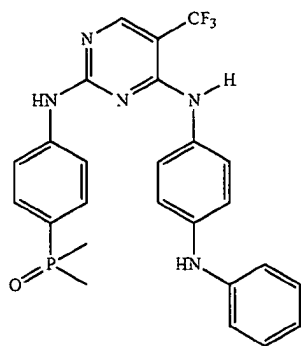
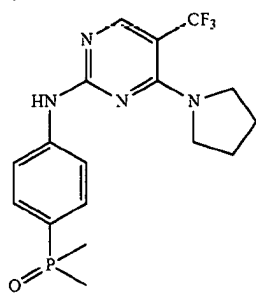
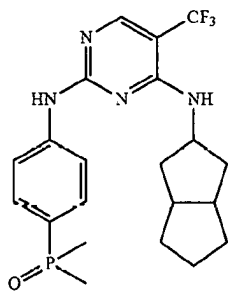
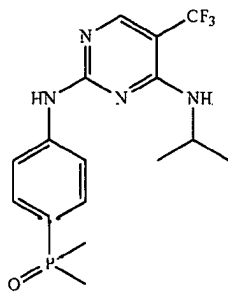
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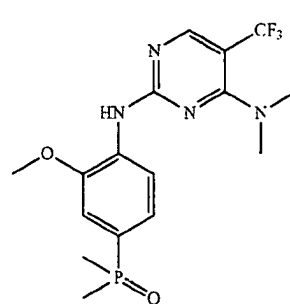
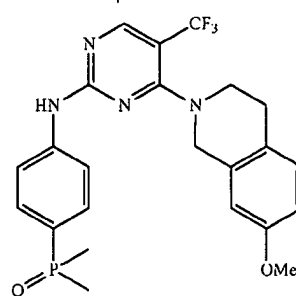
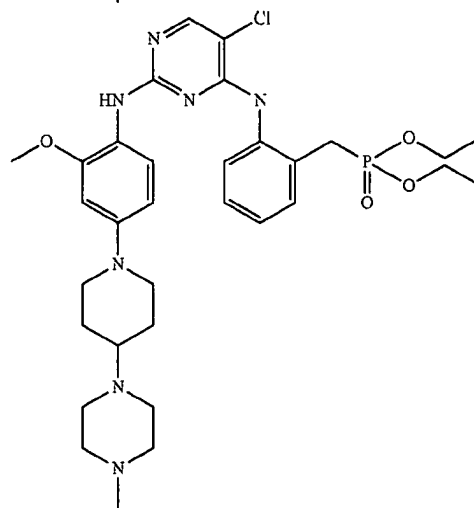
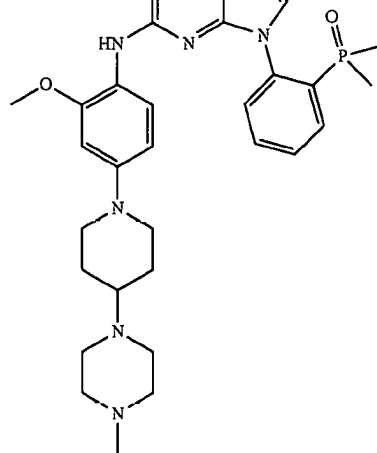
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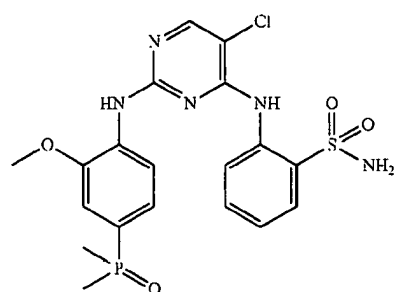
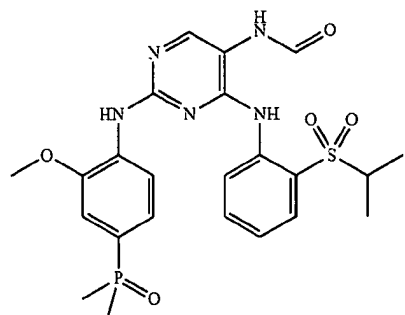
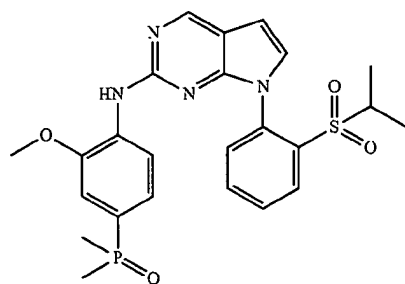
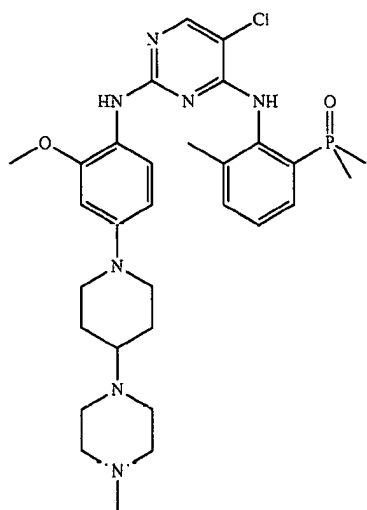
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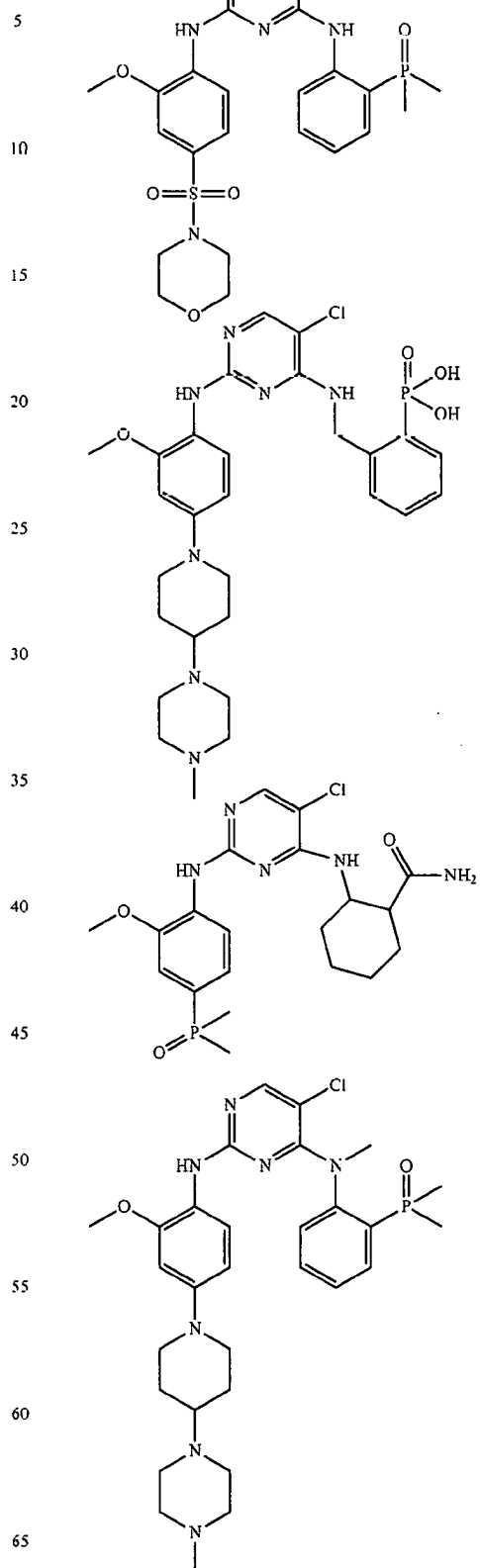


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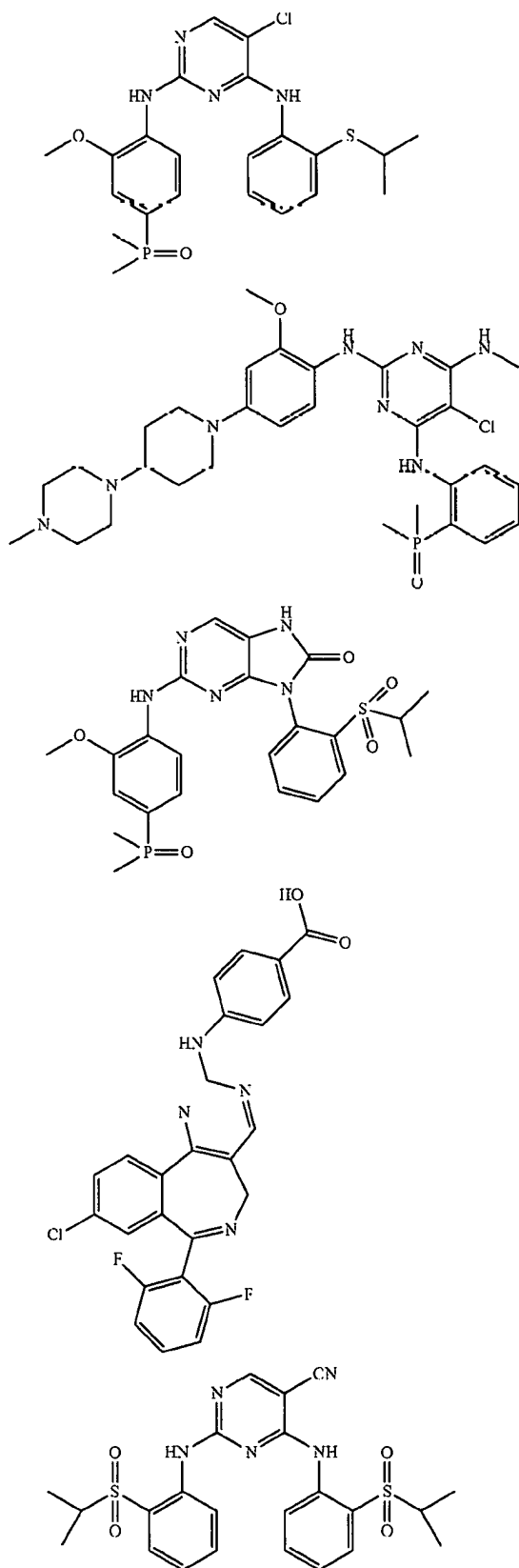
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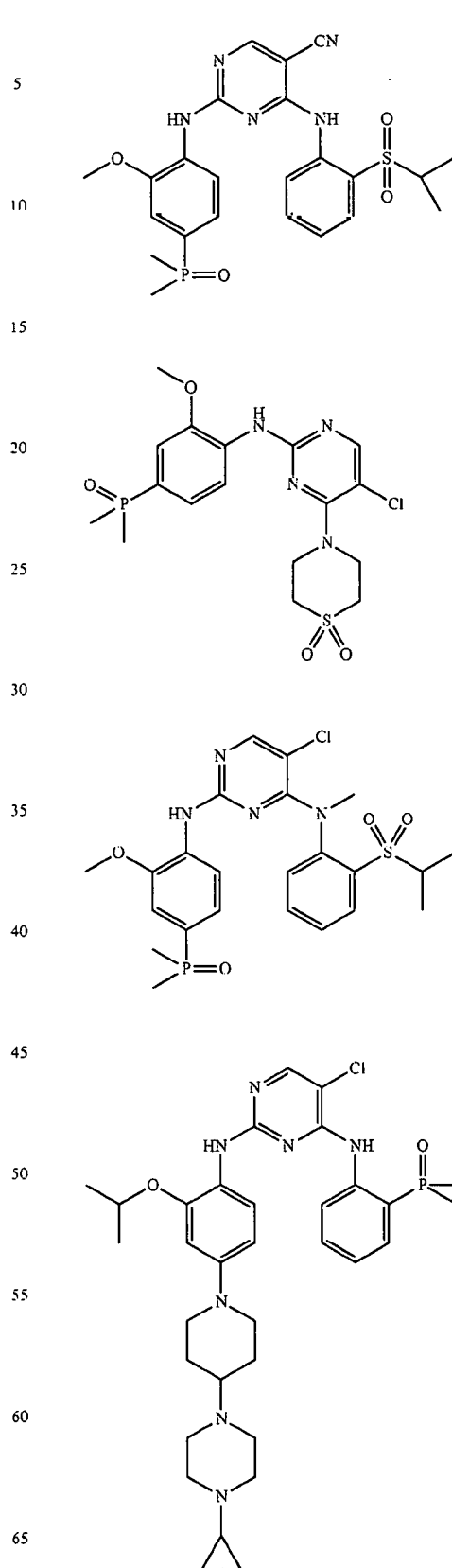


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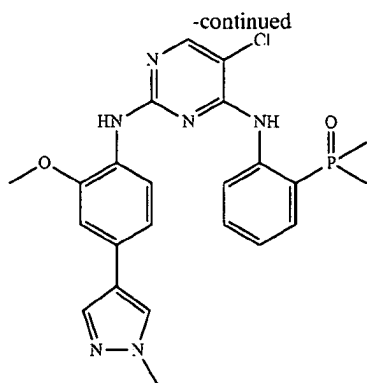
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Kinase Inhibition

More specifically, the compounds described herein are screened for kinase inhibition activity as follows. Kinases suitable for use in the following protocol include, but are not limited to: ALK, Jak2, b-Raf, c-Met, Tie-2, FLT3, Abl, Lek, Lyn, Src, Fyn, Syk, Zap-70, Itk, Tec, Btk, EGFR, ErbB2, Kdr, FLT1, Tek, InsR, and AKT.

Kinases are expressed as either kinase domains or full length constructs fused to glutathione S-transferase (GST) or polyHistidine tagged fusion proteins in either *E. coli* or Baculovirus-High Five expression systems. They are purified to near homogeneity by affinity chromatography as previously described (Lehr et al., 1996; Gish et al., 1995). In some instances, kinases are co-expressed or mixed with purified or partially purified regulatory polypeptides prior to measurement of activity.

Kinase activity and inhibition can be measured by established protocols (see e.g., Braunwalder et al., 1996). In such cases, the transfer of ^{32}P from ATP to the synthetic substrates poly(Glu, Tyr) 4:1 or poly(Arg, Ser) 3:1 attached to the bioactive surface of microtiter plates is taken as a measure of enzyme activity. After an incubation period, the amount of phosphate transferred is measured by first washing the plate with 0.5% phosphoric acid, adding liquid scintillant, and then counting in a liquid scintillation detector. The IC_{50} is determined by the concentration of compound that causes a 50% reduction in the amount of ^{32}P incorporated onto the substrate bound to the plate.

Other methods relying upon the transfer of phosphate to peptide or polypeptide substrate containing tyrosine, serine, threonine or histidine, alone, in combination with each other, or in combination with other amino acids, in solution or immobilized (i.e., solid phase) are also useful.

For example, transfer of phosphate to a peptide or polypeptide can also be detected using scintillation proximity, Fluorescence Polarization and homogeneous time-resolved fluorescence.

Alternatively, kinase activity can be measured using antibody-based methods in which an antibody or polypeptide is used as a reagent to detect phosphorylated target polypeptide.

For additional background information on such assay methodologies, see e.g., Braunwalder et al., 1996, *Anal. Biochem.* 234(1):23; Cleaveland et al., 1990, *Anal. Biochem.* 190(2):249; Gish et al. (1995), *Protein Eng.* 8(6):609; Kolb et al. (1998), *Drug Discov. Toda V.* 3:333; Lehr et al. (1996), *Gene* 169(2):27527-87; Seethala et al. (1998), *Anal. Biochem.* 255(2):257; Wu et al. (2000).

The inhibition of ALK tyrosine kinase activity can be demonstrated using known methods. For example, in one method, compounds can be tested for their ability to inhibit kinase

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activity of baculovirus-expressed ALK using a modification of the ELISA protocol reported for trkA in Angeles, T. S. et al., *Anal. Biochem.* 1996, 236, 49-55, which is incorporated herein by reference. Phosphorylation of the substrate, phospholipase C-gamma (PLC- γ) generated as a fusion protein with glutathione-S-transferase (GST) as reported in rotin, D. et al., *EMBO J.* 1992, 11, 559-567, which is incorporated by reference, can be detected with europium-labeled anti-phosphotyrosine antibody and measured by time-resolved fluorescence (TRF). In this assay, 96-well plate is coated with 100 μL /well of 10 $\mu\text{g}/\text{mL}$ substrate (phospholipase C- γ in tris-buffered saline (TBS). The assay mixture (total volume=1004/well) consisting of 20 nM HEPES (pH 7.2, 1 μM ATP (K_m level), 5 nM MnCl_2 , 0.1% BSA, 2.5% DMSO, and various concentrations of test compound is then added to the assay plate. The reaction is initiated by adding the enzyme (30 ng/mL ALK) and is allowed to proceed at 37 degrees C. for 15 minutes. Detection of the phosphorylated product can be performed by adding 100 μL /well of Eu-NI labeled PT66 antibody (Perkin Elmer #AD0041). Incubation at 37 degrees C. then proceeds for one hour, followed by addition of 100 μL enhancement solution (for example Wallac #1244-105). The plate is gently agitated and after thirty minutes, the fluorescence of the resulting solution can be measured (for example using EnVision 2100 (or 2102) multilabel plate reader from Perkin Elmer).

Data analysis can then be performed. IC_{50} values can be calculated by plotting percent inhibition versus $\log_{10}$ of concentration of compound.

The inhibition of ALK tyrosine kinase activity can also be measured using the recombinant kinase domain of the ALK in analogy to VEDG-R kinase assay described in J. Wood et al., *Cancer Res* 2000, 60, 2178-2189. In vitro enzyme assays using GST-ALK protein tyrosine kinase can be performed in 96-well plate as a filter binding assay in 20 mM Tris.HCl, pH 7.5, 3 mM MgCl_2 , 10 mM MnCl_2 , 1 nM DTT, 0.1 $\mu\text{Ci}/\text{assay}$ ($\approx 30 \mu\text{L}$) [γ - ^{32}P]-ATP, 2 μM ATP, 3 $\mu\text{g}/\text{mL}$ poly (Glu, tyr 4:1) Poly-EY (sigma P-0275), 1% DMSO, 25 ng ALK enzyme. Assays can be incubated for 10 min, at ambient temperature. Reactions can be terminated by adding 50 μL of 125 mM EDTA, and the reaction mixture can be transferred onto a MAIP Multiscreen plate (Millipore, Bedford, Mass.) previously wet with methanol, and rehydrated for 5 minutes with water. Following washing (0.5% H_3PO_4), plates can be counted in a liquid scintillation counter. IC_{50} values are calculated by linear regression analysis of the percentage inhibition.

Cell-Based Assays

Certain compounds of the invention have also been demonstrated cytotoxic or growth inhibitory effects on tumor and other cancer cell lines and thus may be useful in the treatment of cancer and other cell proliferative diseases. Compounds are assayed for anti-tumor activity using in vivo and in vitro assays which are well known to those skilled in the art. Generally, initial screens of compounds to identify candidate anti-cancer drugs are performed in cellular assays. Compounds identified as having anti-proliferative activity in such cell-based assays can then be subsequently assayed in whole organisms for anti-tumor activity and toxicity. Generally speaking, cell-based screens can be performed more rapidly and cost-effectively relative to assays that use whole organisms. For purposes of the invention, the terms "anti-tumor" and "anti-cancer" activity are used interchangeably.

Cell-based methods for measuring antiproliferative activity are well known and can be used for comparative characterization of compounds of the invention. In general, cell

proliferation and cell viability assays are designed to provide a detectable signal when cells are metabolically active.

Compounds may be tested for antiproliferative activity by measuring any observed decrease in metabolic activity of the cells after exposure of the cells to compound. Commonly used methods include, for example, measurement of membrane integrity (as a measure of cell viability) (e.g. using trypan blue exclusion) or measurement of DNA synthesis (e.g. by measuring incorporation of BrdU or 3H-thymidine).

Some methods for assaying cell proliferation use a reagent that is converted into a detectable compound during cell proliferation. Particularly preferred compounds are tetrazolium salts and include without limitation MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; Sigma-Aldrich, St. Louis, Mo.), MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium), XTT (2,3-bis(2-Methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide), INT, NBT, and NTV (Bernas et al. *Biochim Biophys Acta* 1451(1):73-81, 1999). More commonly used assays utilizing tetrazolium salts detect cell proliferation by detecting the product of the enzymatic conversion of the tetrazolium salts into blue formazan derivatives, which are readily detected by spectroscopic methods (Mosman. *J. Immunol. Methods*. 65:55-63, 1983).

Other methods for assaying cell proliferation involve incubating cells in a desired growth medium with and without the compounds to be tested. Growth conditions for various prokaryotic and eukaryotic cells are well-known to those of ordinary skill in the art (Ausubel et al. *Current Protocols in Molecular Biology*. Wiley and Sons. 1999; Bonifacino et al. *Current Protocols in Cell Biology*. Wiley and Sons. 1999 both incorporated herein by reference). To detect cell proliferation, the tetrazolium salts are added to the incubated cultured cells to allow enzymatic conversion to the detectable product by active cells. Cells are processed, and the optical density of the cells is determined to measure the amount of formazan derivatives. Furthermore, commercially available kits, including reagents and protocols, are available for examples, from Promega Corporation (Madison, Wis.), Sigma-Aldrich (St. Louis, Mo.), and Trevigen (Gaithersburg, Md.).

In addition, a wide variety of cell types may be used to screen compounds for antiproliferative activity, including the following cell lines, among others: COLO 205 (colon cancer), DLD-1 (colon cancer), HCT-15 (colon cancer), HT29 (colon cancer), HEP G2 (Hepatoma), K-562 (Leukemia), A549 (Lung), NCI-H249 (Lung), MCF7 (Mammary), MDA-MB-231 (Mammary), SAOS-2 (Osteosarcoma), OVCAR-3 (Ovarian), PANC-1 (Pancreas), DU-145 (Prostate), PC-3 (Prostate), ACHN (Renal), CAKI-1 (Renal), MG-63 (Sarcoma).

While the cell line is preferably mammalian, lower order eukaryotic cells such as yeast may also be used to screen compounds. Preferred mammalian cell lines are derived from humans, rats, mice, rabbits, monkeys, hamsters, and guinea pigs since cells lines from these organisms are well-studied and characterized. However, others may be used as well.

Suitable mammalian cell lines are often derived from tumors. For example, the following tumor cell-types may be sources of cells for culturing cells: melanoma, myeloid leukemia, carcinomas of the lung, breast, ovaries, colon, kidney, prostate, pancreas and testes), cardiomyocytes, endothelial cells, epithelial cells, lymphocytes (T-cell and B cell), mast cells, eosinophils, vascular intimal cells, hepatocytes, leukocytes including mononuclear leukocytes, stem cells such as haemopoietic, neural, skin, lung, kidney, liver and myocyte stem cells (for use in screening for differentiation and de-

differentiation factors), osteoclasts, chondrocytes and other connective tissue cells, keratinocytes, melanocytes, liver cells, kidney cells, and adipocytes. Non-limiting examples of mammalian cells lines that have been widely used by researchers include HeLa, NIH/3T3, HT1080, CHO, COS-1, 293T, WI-38 and CV1/EBNA-1.

Other cellular assays may be used which rely upon a reporter gene to detect metabolically active cells. Non-limiting examples of reporter gene expression systems include green fluorescent protein (GFP), and luciferase. As an example of the use of GFP to screen for potential antitumor drugs, Sandman et al. (*Chem. Biol.* 6:541-51; incorporated herein by reference) used HeLa cells containing an inducible variant of GFP to detect compounds that inhibited expression of the GFP, and thus inhibited cell proliferation.

An example of cell-based assay is shown as below. The cell lines that can be used in the assay are Ba/F3, a murine pro-B cell line, which has been stably transfected with an expression vector pCneoTM (Promega Corp., Madison Wis.) coding for NPM-ALK and subsequent selection of G418 resistant cells. Non-transfected Ba/F3 cells depend on IL-3 for cell survival. In contrast NPM-ALK expressing Ba/F3 cells (named Ba/F3-NPM-ALK) can proliferate in the absence of IL-3 because they obtain proliferative signal through NPM-ALK kinase. Putative inhibitors of NPM-ALK kinase therefore abolish the growth signal and result in antiproliferative activity. The antiproliferative activity of inhibitors of the NPM-ALK kinase can however be overcome by addition of IL-3 which provides growth signals through an NPM-ALK independent mechanism. For an analogous cell system using FLT3 kinase see E. Weisberg et al. *Cancer cell*, 2002, 1, 433-443. The inhibitory activity of the compounds of formula I can be determined as follows: BaF3-NPM-ALK cells (15,000/microtitre plate well) can be transferred to a 96-well microtitre plates. The test compound (dissolved in DMSO) is then added in a series of concentrations (dilution series) in such a manner that the final concentration of DMSO is not greater than 1% (v/v). After the addition, the plates can be incubated for two days during which the control cultures without test compound are able to undergo two cell-division cycles. The growth of BaF3-NPM-ALK cells can be measured by means of YoproTM staining (T Idziorek et al., *J. Immunol. Methods* 1995, 185, 249-258). 25 μ L of lysis buffer consisting of 20 mM sodium citrate, pH 4.0, 26.8 mM sodium chloride, 0.4% NP40, 20 mM EDTA and 20 mM is added into each well. Cell lysis is completed within 60 minutes at room temperature and total amount of Yopro bound to DNA is determined by measurement using for example a CytoFluor II 96-well reader (PerSeptive Biosystems). The IC₅₀ can be determined by a computer aided system using the formula:

$$IC_{50} = \frac{(ABS_{test} - ABS_{start})}{(ABS_{control} - ABS_{start})} \times 100$$

in which ABS is absorption. The IC₅₀ value in such an experiment is given as that concentration of the test compound in question that results in a cell count that is 50% lower than that obtained using the control without inhibitor.

The antiproliferative action of compounds of the invention can also be determined in the human KARPAS-299 lymphoma cell line by means of an immunoblot as described in W G Dirks et al. *Int. J. Cancer* 2002, 100, 49-56., using the methodology described above for the BaF3-NPM-ALK cell line.

In another example, antiproliferative activity can be determined using KARPAS-299 lymphoma cell line in the following procedure: Compounds of the invention were incubated with the cells for 3 days, and the number of viable cells in each well was measured indirectly using an MTS tetrazolium

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assay (Promega). This assay is a colorimetric method for determining the number of viable cells through measurement of their metabolic activity. For example the detection of the product of the enzymatic conversion of tetrazolium salts into blue formazan derivatives is achieved by measuring absorbance at 490 nm using a plate reader. 40 μ L of the MTS reagent was added to all wells except the edge wells and then the plates were returned to the incubator at 37° C. for 2 hours. The absorbance in each well was then measured at 490 nm using a Wallac Victor³V plate reader. The IC_{50} was calculated by determining the concentration of compound required to decrease the MTS signal by 50% in best-fit curves using Microsoft XLfit software, by comparing with baseline, the DMSO control, as 0% inhibition.

Compounds identified by such cellular assays as having anti-cell proliferation activity are then tested for anti-tumor activity in whole organisms. Preferably, the organisms are mammalian. Well-characterized mammalian systems for studying cancer include rodents such as rats and mice. Typically, a tumor of interest is transplanted into a mouse having a reduced ability to mount an immune response to the tumor to reduce the likelihood of rejection. Such mice include for example, nude mice (athymic) and SCID (severe combined immunodeficiency) mice. Other transgenic mice such as oncogene containing mice may be used in the present assays (see for example U.S. Pat. No. 4,736,866 and U.S. Pat. No. 5,175,383). For a review and discussion on the use of rodent models for antitumor drug testing see Kerbel (Cancer Metastasis Rev. 17:301-304, 1998-99).

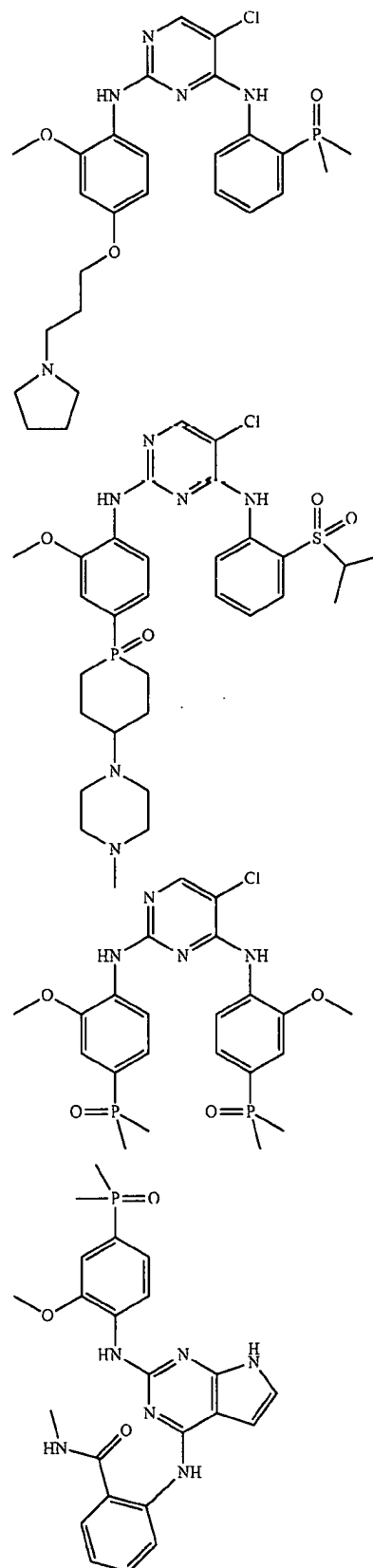
In general, the tumors of interest are implanted in a test organism preferably subcutaneously. The organism containing the tumor is treated with doses of candidate anti-tumor compounds. The size of the tumor is periodically measured to determine the effects of the test compound on the tumor. Some tumor types are implanted at sites other than subcutaneous sites (e.g. intraperitoneal sites) and survival is measured as the endpoint. Parameters to be assayed with routine screening include different tumor models, various tumor and drug routes, and dose amounts and schedule. For a review of the use of mice in detecting antitumor compounds see Corbett et al. (Invest New Drugs. 15:207-218, 1997; incorporated herein by reference).

Results

A wide variety of compounds of this invention were found to potentially inhibit a number of important kinase targets. Many exhibited IC_{50} 's under 100 nM, and in many cases under 10 nM and in some cases under 1 nM when tested as inhibitors of the kinase, ALK, for instance. Those included compounds containing the phosphine oxide moiety as an R^a or R^c substituent as well as compounds in which positions X^3 and X^4 were the base of a substituted or unsubstituted fused ring which is present in a number of embodiments. Some compounds were single digit nanomolar inhibitors of a panel of kinases including kinases like ALK, FER, FLT3, FES/FPS, FAK/PTK2, BRK and others. Compounds of the invention of various structures were found to exhibit preferences for inhibiting some kinases over others as well as variations in pharmacokinetic profiles, confirming that this class of compounds is of great interest as a source of potential pharmaceutical agents.

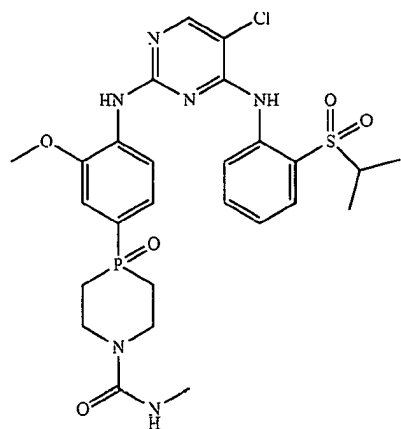
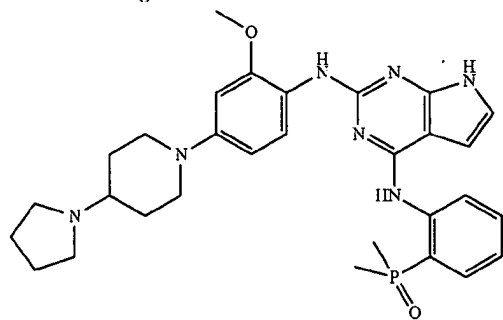
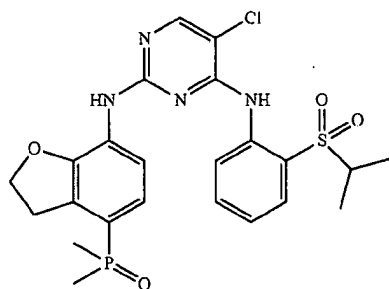
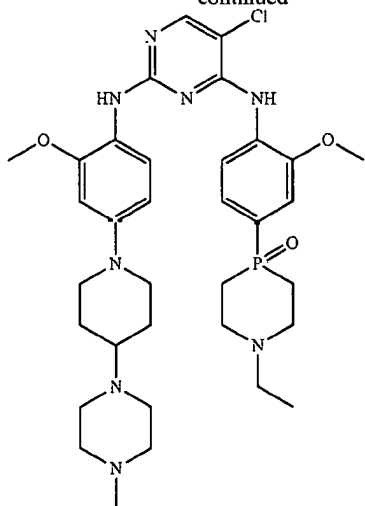
To illustrate the foregoing, a varied group of compounds (shown below) were tested and found to have IC_{50} values under 1 nM when tested against the kinase ALK.

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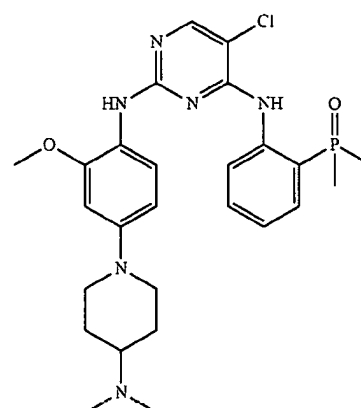
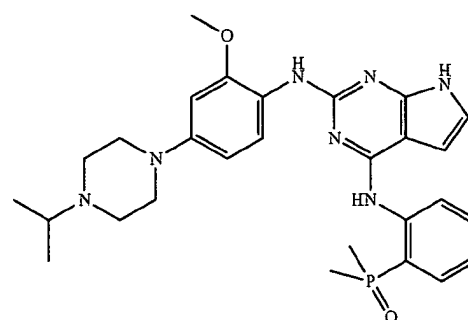
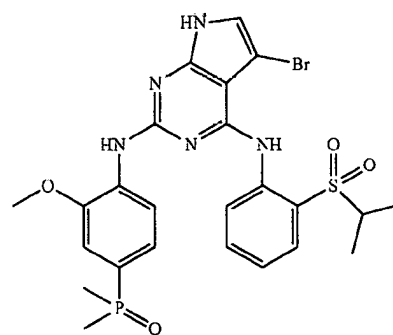
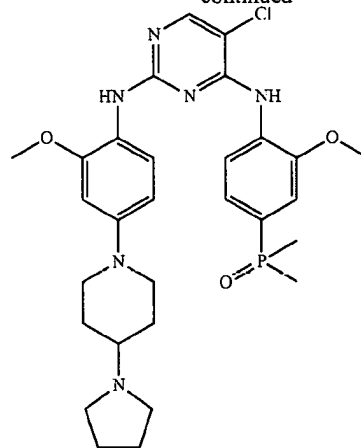
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Example 21

Pharmaceutical Compositions

Representative pharmaceutical dosage forms of compounds of the invention (the active ingredient being referred to as "Compound"), are provided for therapeutic or prophylactic use in humans:

(a) Tablet I	mg/tablet
Compound	100
Lactose Ph. Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b) Tablet II	mg/tablet
Compound	50
Lactose Ph. Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c) Tablet III	mg/tablet
Compound	1.0
Lactose Ph. Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0-76

(d) Capsule	mg/capsule
Compound	10
Lactose Ph. Eur	488.5
Magnesium	1.5

(e) Injection I	(50 mg/ml)
Compound	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f) Injection II	(10 mg/ml)
Compound	1.0% W/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III	(1 mg/ml, buffered to pH 6)
Compound	0.1% w/v
Sodium phosphate BP	2.26% w/v

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(g) Injection III	(1 mg/ml, buffered to pH 6)
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

(h) Aerosol I	mg/ml
Compound	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	49.00

(i) Aerosol II	mg/ml
Compound	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j) Aerosol III	mg/ml
Compound	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	19.16

(k) Aerosol IV	mg/ml
Compound	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	108.60
Dichlorotetrafluoroethane	191.6

(l) Ointment	/ml
Compound	40 mg
Ethanol	300 µl
Water	300 µl
1-Dodecylazacycloheptan one	50 µl
Propylene glycol	to 1 ml

These formulations may be prepared using conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, if desired to provide a coating of cellulose acetate phthalate, for example. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

OTHER EMBODIMENTS

All publications, patents, and patent applications mentioned in this specification are incorporated herein by refer-

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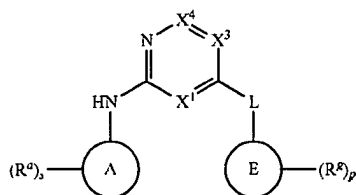
ence to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are within the claims.

The invention claimed is:

1. A compound of the formula:



wherein

X^1 is NR^{b1} or CR^{b1} ;

X^3 is NR^{d1} or CR^{d1} ;

X^4 is NR^{e1} or CR^{e1} ;

Ring A and Ring E are each an independently selected aryl or heteroaryl ring, the heteroaryl ring being a 5- or 6-membered ring containing 1 to 4 heteroatoms selected from N, O and S(O)_n;

each R^a , R^b , R^d , R^e , and R^s is independently halo, —CN, —NO₂, —R¹, —OR², —O—NR¹R², —NR¹R², —NR¹—NR¹R², —NR¹—OR², —C(O)YR², —OC(O)YR², —NR¹C(O)YR², —SC(O)YR², —NR¹C(=S)YR², —OC(=S)YR², —C(=S)YR², —YC(=NR¹)YR², —YC(=N—OR¹)YR², —YC(=N—NR¹R²)YR², —YP(=O)(YR³)(YR³), —Si(R^{3a})₃, —NR¹SO₂R², —S(O)₁R², —SO₂NR¹R² or —NR¹SO₂NR¹R²; provided that at least one of R^a and R^s is or includes —P(=O)(R³)₂ or a ring system containing —P(=O)(R³)₂ as a ring member;

and R^{b1} , R^{d1} and R^{e1} are absent;

or alternatively two adjacent substituents selected from R^d , R^{d1} , R^e , and R^{e1} , or two adjacent R^a form, with the atoms to which they are attached, a fused, 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4 heteroatoms selected from N, O and S(O)_n, and which may bear up to four substituents;

L is O or NH;

r is 0, 1 or 2;

s is 1, 2, 3, 4 or 5;

p is 1, 2, 3 or 4;

each Y is independently a bond, —O—, —S— or —NR¹—;

each R¹ and R² is independently H or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl;

each R³ is independently an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl, or two adjacent R³ combine to form a ring system including a phosphorous atom;

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each R^{3a} is independently an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic, or heteroaryl;

alternatively, each NR¹R² may be a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which can be optionally substituted and which contains 0-2 additional heteroatoms selected from N, O and S(O)_n; and

each of the foregoing alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocyclic is optionally substituted,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 in which:

(a) X^1 is N, X^3 is N and X^4 is CR^{e1} ;

(b) X^1 is N, X^3 is CR^{d1} and X^4 is CR^{e1} ;

(c) X^1 is CR^{b1} , X^3 is N and X^4 is CR^{d1} , or

(d) X^1 is CR^{b1} , X^3 is CR^{d1} and X^4 is Cr.

3. The compound of claim 1 in which R^d is selected from Cl, F, C1-C4 alkyl, trihaloalkyl, cycloalkyl, C2-C4 alkenyl, and alkynyl

4. The compound of claim 1 in which X^3 is CR^{d1} and X^4 is CR^{e1} wherein R^d and R^e , together with the atoms to which they are attached, form a fused, 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, which contains 0-4 heteroatoms selected from N, O and S(O)_n, and which may bear up to four substituents.

5. The compound of claim 1 in which s is 1, 2, 3 or 4, and each of the substituents R^a is independently selected from halo, —R¹, —OR², —NR¹R² and —P(=O)(R³)₂— wherein each R¹ and R² may be further substituted or unsubstituted.

6. The compound of claim 5 in which at least one substituent R^a is —OR² and R² is selected from C1-C6 alkyl, C2-C6 alkenyl, and C2-C6 alkynyl.

7. The compound of claim 5 in which at least one substituent R^a is a 5-, 6- or 7-membered heterocyclic or 5- or 6-membered heteroaryl, linked to Ring A either directly or by an ether bond, and which may be further substituted with 1, 2 or 3 substituents independently selected from halo, —CN, NO₂, R¹, OR², O—NR¹R², NR¹R², NR¹—NR¹R², —NR¹—OR², —C(O)YR², —OC(O)YR², —NR¹C(O)YR², —SC(O)YR², —NR¹C(=S)YR², —OC(=S)YR², —C(=S)YR², —YC(=NR¹)YR², —YC(=N—OR¹)YR², —YC(=N—NR¹R²)YR², —YP(=O)(YR³)(YR³), —Si(R^{3a})₃, —NR¹SO₂R², —S(O)₁R², —SO₂NR¹R² and —NR¹SO₂NR¹R²; wherein each Y is independently a bond, —O—, —S— or —NR¹—.

8. The compound of claim 5 in which at least one substituent R^a is —P(=O)(R³)₂ in which each R³ is, independently, a C1-C4 alkyl.

9. The compound of claim 2 in which:

(a) X^1 is N, X^3 is CR^{d1} and X^4 is CR^{e1} ; or

(b) X^1 is CR^{b1} , X^3 is CR^{d1} and X^4 is CR^{e1} ;

and R^d is selected from Cl, F, C1-C4 alkyl, trihaloalkyl, cycloalkyl, C2-C4 alkenyl, and alkynyl.

10. The compound of claim 2 in which s is 1, 2, 3 or 4, and each of the substituents R^a is independently selected from halo, —R¹, —OR², —NR¹R² and —P(=O)(R³)₂, wherein each R¹ and R² may be further substituted or unsubstituted.

11. The compound of claim 3 in which s is 1, 2, 3 or 4, and each of the substituents R^a is independently selected from halo, —R¹, —OR², —NR¹R² and —P(=O)(R³)₂, wherein each R¹ and R² may be further substituted or unsubstituted.

12. The compound of claim 9 in which s is 1, 2, 3 or 4, and each of the substituents R^a is independently selected from halo, —R¹, —OR², —NR¹R² and —P(=O)(R³)₂, wherein each R¹ and R² may be further substituted or unsubstituted.

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13. The compound of claim 4 in which s is 1, 2, 3 or 4, and each of the substituents R^a is independently selected from halo, $-R^1$, $-OR^2$, $-NR^1R^2$ and $-P(=O)(R^3)_2$, wherein each R^1 and R^2 may be further substituted or unsubstituted.

14. The compound of claim 4 in which at least one substituent R^a is $-OR^2$ and R^2 is selected from C1-C6 alkyl, C2-C6 alkenyl, and C2-C6 alkynyl.

15. The compound of claim 11 in which at least one substituent R^a is $-OR^2$ and R^2 is selected from C1-C6 alkyl, C2-C6 alkenyl, and C2-C6 alkynyl.

16. The compound of claim 12 in which at least one substituent R^a is $-OR^2$ and R^2 is selected from C1-C6 alkyl, C2-C6 alkenyl, and C2-C6 alkynyl.

17. The compound of claim 13 in which at least one substituent R^a is $-OR^2$ and R^2 is selected from C1-C6 alkyl, C2-C6 alkenyl, and C2-C6 alkynyl.

18. The compound of claim 10 in which at least one substituent s is a 5-, 6- or 7-membered heterocyclic or 5- or 6-membered heteroaryl, linked to Ring A either directly or by an ether bond, and which may be further substituted with 1, 2 or 3 substituents independently selected from halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^3)_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$.

19. The compound of claim 11 in which at least one substituent R^a is a 5-, 6- or 7-membered heterocyclic or 5- or 6-membered heteroaryl, linked to Ring A either directly or by an ether bond, and which may be further substituted with 1, 2 or 3 substituents independently selected from halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^3)_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$.

20. The compound of claim 12 in which at least one substituent R^a is a 5-, 6- or 7-membered heterocyclic or 5- or 6-membered heteroaryl, linked to Ring A either directly or by an ether bond, and which may be further substituted with 1, 2 or 3 substituents independently selected from halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^3)_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$.

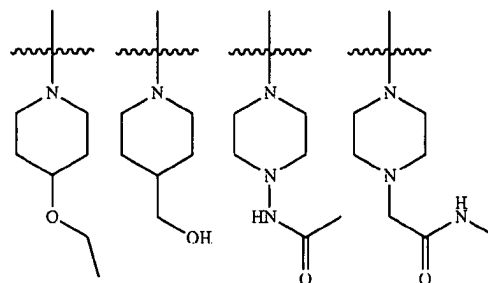
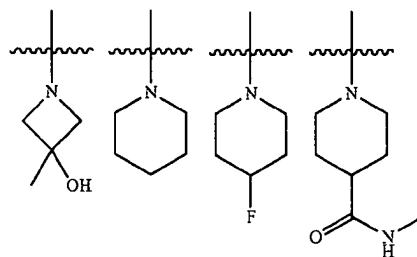
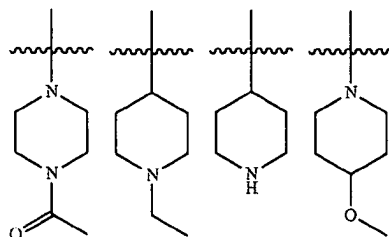
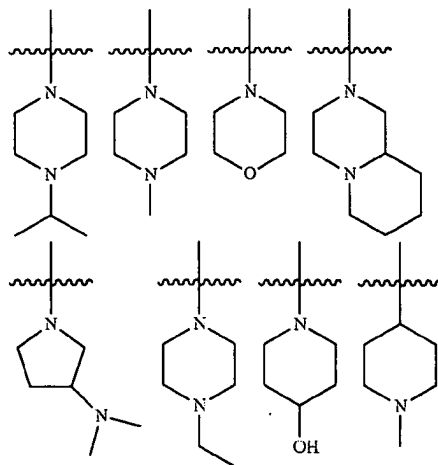
21. The compound of claim 13 in which at least one substituent R^a is a 5-, 6- or 7-membered heterocyclic or 5- or 6-membered heteroaryl, linked to Ring A either directly or by an ether bond, and which may be further substituted with 1, 2 or 3 substituents independently selected from halo, $-CN$, $-NO_2$, $-R^1$, $-OR^2$, $-O-NR^1R^2$, $-NR^1R^2$, $-NR^1-NR^1R^2$, $-NR^1-OR^2$, $-C(O)YR^2$, $-OC(O)YR^2$, $-NR^1C(O)YR^2$, $-SC(O)YR^2$, $-NR^1C(=S)YR^2$, $-OC(=S)YR^2$, $-C(=S)YR^2$, $-YC(=NR^1)YR^2$, $-YC(=N-OR^1)YR^2$, $-YC(=N-NR^1R^2)YR^2$, $-YP(=O)(YR^3)(YR^3)$, $-Si(R^3)_3$, $-NR^1SO_2R^2$, $-S(O)_2R^2$, $-SO_2NR^1R^2$ and $-NR^1SO_2NR^1R^2$; wherein each Y is independently a bond, $-O-$, $-S-$ or $-NR^1-$.

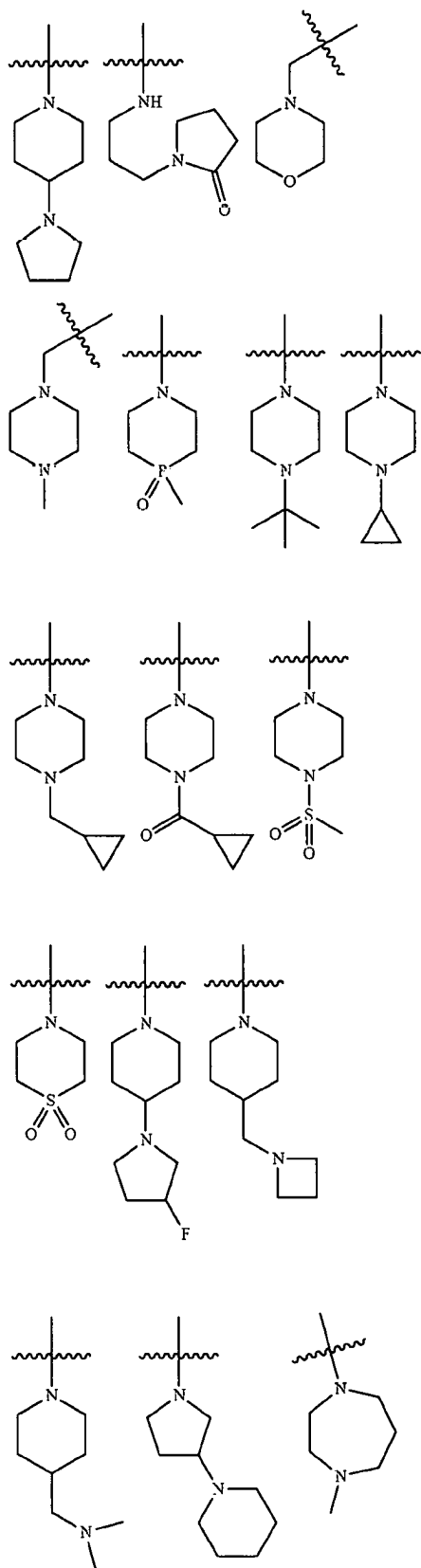
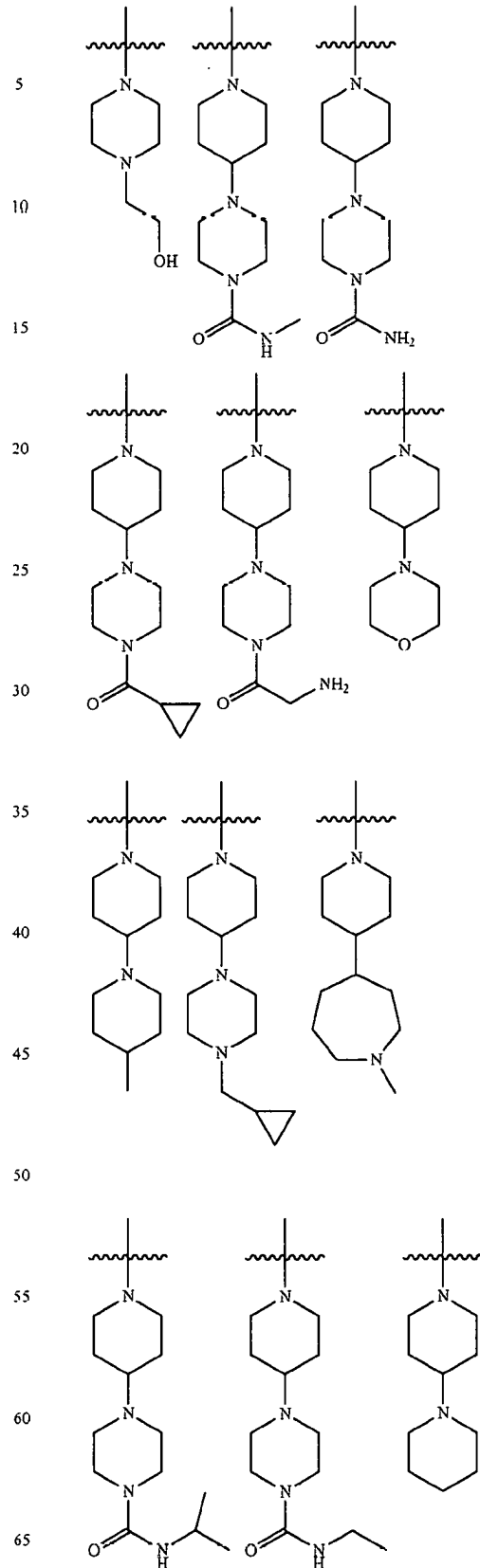
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22. The compound of claim 6 in which at least one substituent R^a is $-P(=O)(R^3)_2$ in which each R^3 is, independently, a C1-C4 alkyl.

23. The compound of claim 7 in which at least one substituent R^a is $P(=O)(R^3)_2$ in which each R^3 is, independently, a C1-C4 alkyl.

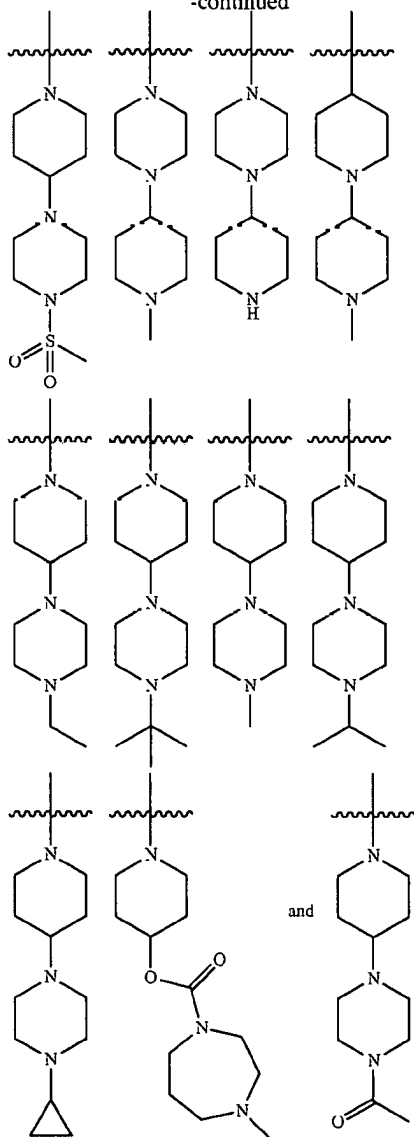
24. The compound of any of claim 7, 18, 19, 20, or 21, in which the heterocyclic or heteroaryl substituent R^a is selected from the following:



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-continued



25. The compound of claim 24 in which at least one substituent R^a is $P(=O)(R^3)_2$ in which each R^3 is, independently, a C1-C4 alkyl.

26. The compound of claim 24 in which L is NH, Ring E is aryl, and each R^g is independently selected from halo, $-R^1$, $-OR^2$, $-S(O)R^2$ and $-P(=O)(R^3)_2$.

27. The compound of claim 25 in which L is NH, Ring E is aryl, and each R^g is independently selected from halo, $-R^1$, $-OR^2$, $-S(O)R^2$ and $-P(=O)(R^3)_2$.

28. The compound of claim 26 in which Ring E contains at least one R^g in the ortho position, relative to the ring atom attached to L.

29. The compound of claim 27 in which Ring E contains at least one R^g in the ortho position, relative to the ring atom attached to L.

30. The compound of claim 26 in which Ring E contains at least one R^g in the meta position, relative to the ring atom attached to L.

31. The compound of claim 27 in which Ring E contains at least one R^g in the meta position, relative to the ring atom attached to L.

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32. The compound of claim 26 in which Ring E contains at least one R^g in the para position, relative to the ring atom attached to L.

33. The compound of claim 27 in which Ring E contains at least one R^g in the para position, relative to the ring atom attached to L.

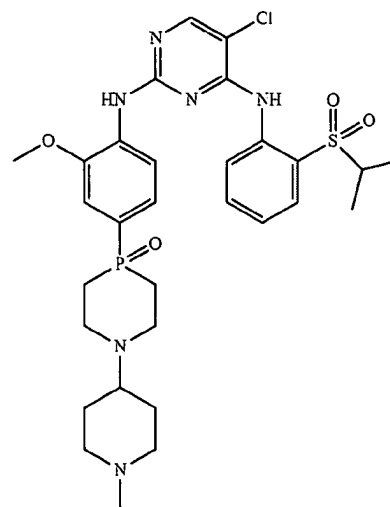
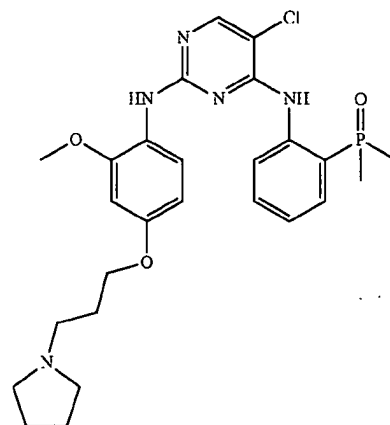
34. A pharmaceutical composition containing a compound of claim 24 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

35. A pharmaceutical composition containing a compound of claim 25 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

36. A pharmaceutical composition containing a compound of claim 26 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

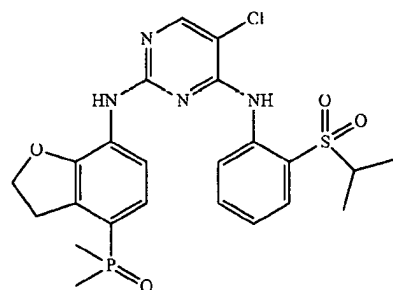
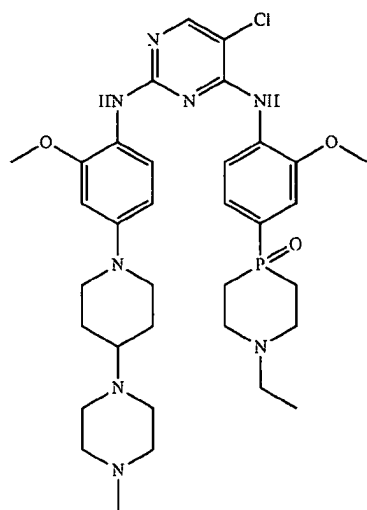
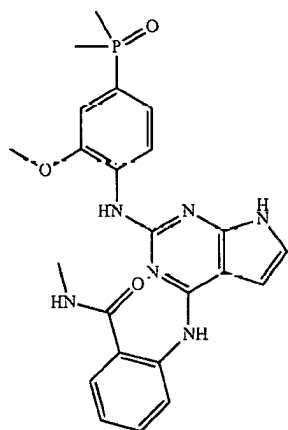
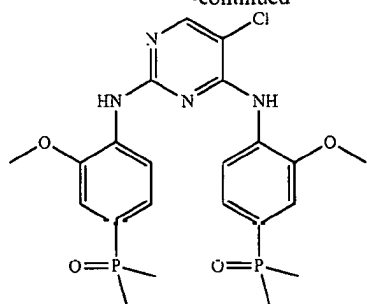
37. A pharmaceutical composition containing a compound of claim 27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

38. The compound of claim 1 selected from the following:



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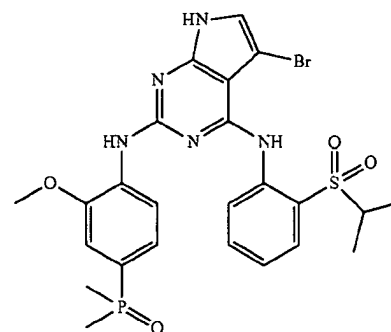
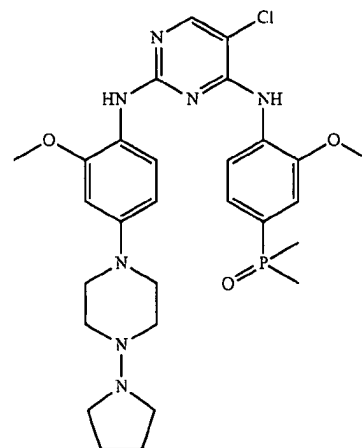
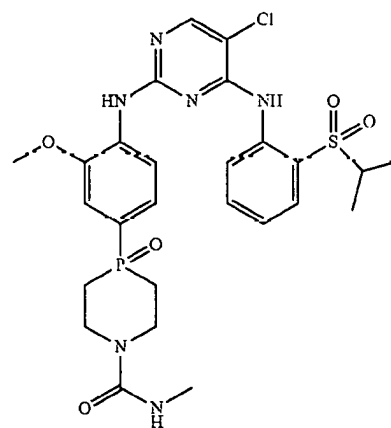
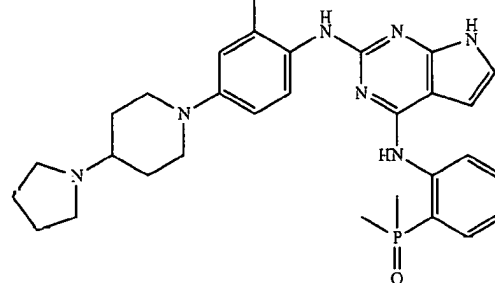
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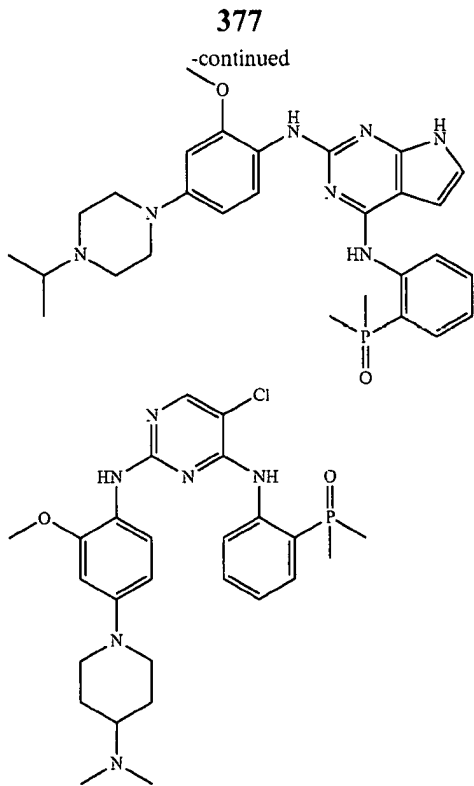
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or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1 selected from the following:

6-chloro-N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-phenyl-1,2,4-triazine-3,5-diamine;

6-chloro-N⁵-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine:

6-chloro-N⁵-[4-(dimethylphosphoryl)phenyl]-N³-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}-1,2,4-triazine-3,5-diamine:

6-chloro-N³-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;

6-chloro-N³-[5-(dimethylphosphoryl)-3-methoxy-pyrazin-2-yl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine:

N⁵-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N³-{2-methoxy-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine;

6-chloro-N³-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine:

6-chloro-N³-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine:

6-chloro-N³-[4-(dimethylphosphoryl)-2-ethylphenyl]-
N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-
diamine:

6-chloro-N³-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;

6-chloro-N³-[2-chloro-4-(dimethylphosphoryl)phenyl]-
N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-
diamine;

6-chloro-N³-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine:



6-chloro-N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;

6-chloro-N³-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}phenyl}-N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine; and

6-chloro-N³-[4-(diethylphosphoryl)-2-methoxyphenyl]-
N⁵-[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-
diamine;

or a pharmaceutically acceptable salt thereof.

40. The compound of claim 1 selected from the following:

5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;

5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[4-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine;

5-chloro-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N²-[5-(propan-2-yl)-1,3-oxazol-2-yl]pyrimidine-2,4-diamine;

5-chloro-N²-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidine-2,4-diamine;

N²-[5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-yl]-5-chloro-N⁴-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]pyrimidine-2,4-diamine;

5-chloro-N⁴-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N²-{5-[4-(pyridin-2-yl)piperazin-1-yl]-1,3,4-oxadiazol-2-yl}pyrimidine-2,4-diamine;

5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine:

5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidine-2,4-diamine:

5-chloro-N²-(2-cyclopropyl-1,3-oxazol-5-yl)-N⁴-[4-(diethylphosphoryl)-2-methoxyphenyl]pyrimidine-2,4-diamine:

N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-4,6-diamine:

6-chloro-N⁵-[4-(dimethylphosphoryl)phenyl]-N'-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]-1,2,4-triazine-3,5-diamine;

N⁵-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N'-{2-methoxy-[4(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine; and,

5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;

or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1 selected from the following:
N⁴-(3,5-dimethylphenyl)-N²-[4-(dimethylphosphoryl)]

phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine;
5-chloro-N²-(4-(dimethylphosphoryl)-2-methoxyphenyl)-N⁴-phenylpyrimidine-2,4-diamine;

N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine;

5-chloro-N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;

5-chloro-N²-[4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;

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5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-Chloro-N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-Chloro-N²-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-Chloro-N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-Chloro-N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-Chloro-N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-Chloro-N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4,5-triamine;
 N²-[2-methoxy-4-(4-oxido-1,4-azaphosphinan-4-yl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine;
 5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-chloro-N²-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-phenylpyrimidine-2,4-diamine;
 N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine;
 N²-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine;
 5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[4-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine;
 5-chloro-N²-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-ethoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidine-2,4-diamine;
 N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-5-methyl-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine;
 5-chloro-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N²-[5-(propan-2-yl)-1,3-oxazol-2-yl]pyrimidine-2,4-diamine;
 5-chloro-N²-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-N⁴-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]pyrimidine-2,4-diamine;

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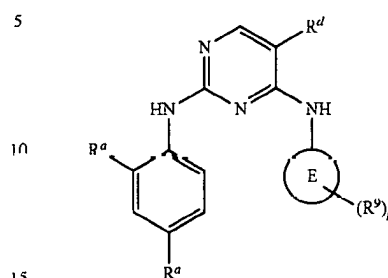
N²-[5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-yl]-5-chloro-N⁴-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]pyrimidine-2,4-diamine;
 5-chloro-N⁴-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N²-[5-[4-(pyridin-2-yl)piperazin-1-yl]-1,3,4-oxadiazol-2-yl]pyrimidine-2,4-diamine-4;
 5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-[2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl]pyrimidine-2,4-diamine;
 5-chloro-N²-(5-cyclopropyl-1,3-oxazol-2-yl)-N⁴-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]pyrimidine-2,4-diamine;
 5-chloro-N²-(2-cyclopropyl-1,3-oxazol-5-yl)-N⁴-[4-(diethylphosphoryl)-2-methoxyphenyl]pyrimidine-2,4-diamine;
 N-(3,5-dimethylphenyl)-N⁴-[4-(dimethylphosphoryl)phenyl]pyrimidine-4,6-diamine;
 N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-2-methyl-N⁴-phenylpyrimidine-4,6-diamine;
 N³-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-5-[3-fluoro-5-(trifluoromethyl)phenoxy]pyridazin-3-amine;
 N-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine;
 N-[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine;
 N-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-4,6-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[5-(dimethylphosphoryl)-2-methoxyphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-methylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-ethylphenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[2-chloro-4-(dimethylphosphoryl)phenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N²-[4-(dimethylphosphoryl)-2-fluorophenyl]-N⁴-[2-(propan-2-ylsulfonyl)phenyl]-5-(trifluoromethyl)pyridine-2,4-diamine;
 N-[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]-N⁴-[2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidine-4,6-diamine;
 N³-[4-(1-ethyl-4-oxido-1,4-azaphosphinan-4-yl)-2-methoxyphenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N³-[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]-N⁵-[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;

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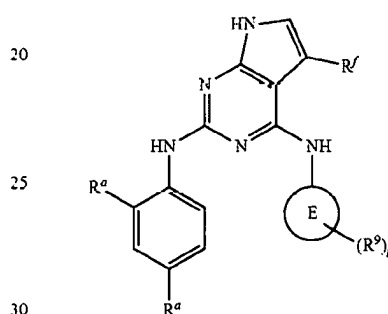
N^3 -{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}- N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 N^3 -[4-(diethylphosphoryl)-2-methoxyphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]pyridazine-3,5-diamine;
 6-chloro- N^3 -[4-(dimethylphosphoryl)-2-methoxyphenyl]- N^5 -phenyl-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[4-(dimethylphosphoryl)-2-methoxyphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^5 -[4-(dimethylphosphoryl)phenyl]- N^3 -{2-methoxy-4-[4-(4-ethylpiperazin-1-yl)piperidin-1-yl]phenyl}-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[5-(dimethylphosphoryl)-3-methoxypyrazin-2-yl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 N^5 -[4-(dimethylphosphoryl)-2-(propan-2-ylsulfonyl)phenyl]- N^3 -{2-methoxy-4-[4-(4-methylpiperazin-1-yl)sulfonyl]phenyl}-6-methyl-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[5-(dimethylphosphoryl)-2-methoxyphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[4-(dimethylphosphoryl)-2-methylphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[4-(dimethylphosphoryl)-2-ethylphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[4-(dimethylphosphoryl)-2-(trifluoromethoxy)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[2-chloro-4-(dimethylphosphoryl)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[4-(dimethylphosphoryl)-2-fluorophenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[2-methoxy-4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)phenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -{2-methoxy-4-[4-(4-methyl-4-oxido-1,4-azaphosphinan-1-yl)piperidin-1-yl]phenyl}- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine;
 6-chloro- N^3 -[4-(diethylphosphoryl)-2-methoxyphenyl]- N^5 -[2-(propan-2-ylsulfonyl)phenyl]-1,2,4-triazine-3,5-diamine; and,
 5-chloro- N^4 -[2-(dimethylphosphoryl)phenyl]- N^2 -{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine;
 or a pharmaceutically acceptable salt thereof.

42. The compound of claim 1 of Formula VIA-i or Formula VIA-ii:

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VIA-i



VIA-ii

43. The compound of claim 42 in which the ortho R^a is H, halo, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 haloalkoxy or $-P(O)(R^3)_2$.

44. The compound of claim 42 in which R^a is F, Cl, C1-C4 alkyl, cyclopropyl, CF_3 , OMe, or OCF_3 , or R' is H, $-CH_3$ or halo.

45. The compound of claim 43 in which R^a is F, Cl, C1-C4 alkyl, cyclopropyl, CF_3 , OMe, or OCF_3 , or R' is H, $-CH_3$ or halo.

46. The compound of claim 42 in which Ring E is aryl, and each R^8 is independently $-SO_2CH_3$, $-SO_2-iPr$, $-SO_2NH-iPr$, $-SONH-nPr$, $-SO_2NEt_2$, $-P(O)(CH_3)_2$, $-P(O)(Et)_2$, $-P(O)(Pr)_2$, Me, OMe, $-O-iPr$, $-OCF_3$, CN, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, or $-C(O)NH-iPr$.

47. The compound of claim 43 in which Ring E is aryl, and each R^8 is independently $-SO_2CH_3$, $-SO_2-iPr$, $-SO_2NH-iPr$, $-SONH-nPr$, $-SO_2NEt_2$, $-P(O)(CH_3)_2$, $-P(O)(Et)_2$, $-P(O)(Pr)_2$, Me, OMe, $-OCF_3$, CN, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, or $-C(O)NH-iPr$.

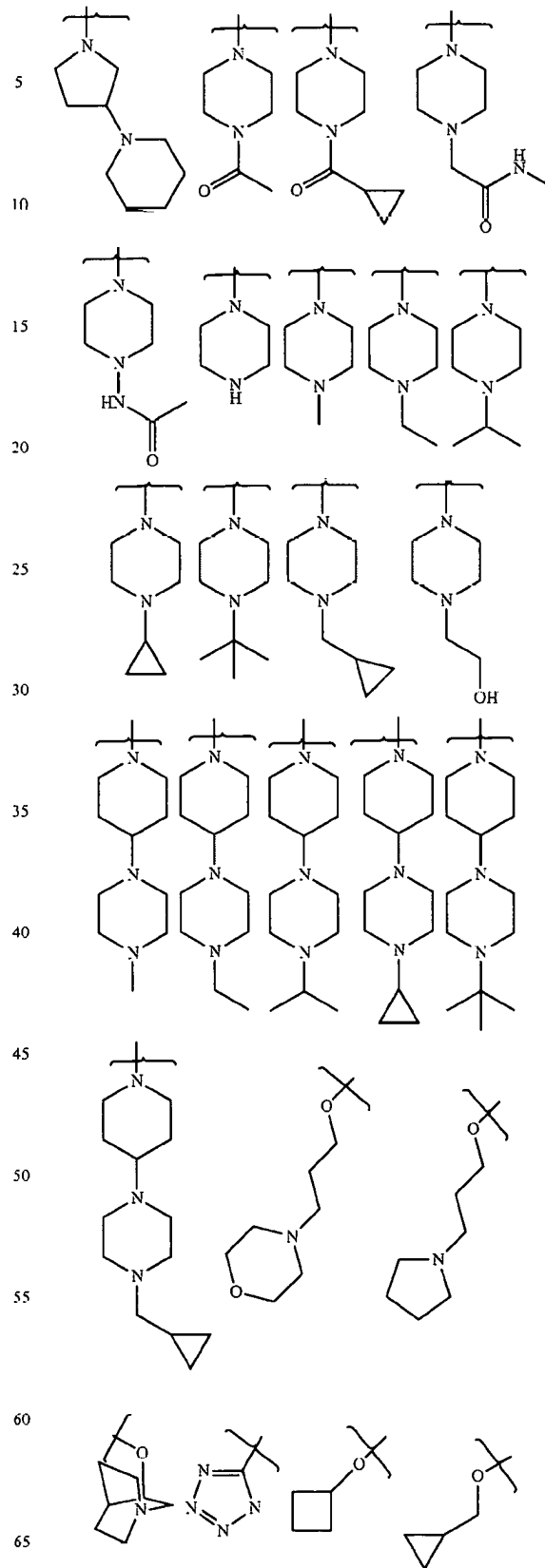
48. The compound of claim 44 in which Ring E is aryl, and each R^8 is independently $-SO_2CH_3$, $-SO_2NH-iPr$, $-SONH-nPr$, $-SO_2NEt_2$, $-P(O)(CH_3)_2$, $-P(O)(Et)_2$, $-P(O)(Pr)_2$, Me, OMe, $-OCF_3$, CN, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, or $-C(O)NH-iPr$.

49. The compound of claim 45 in which Ring E is aryl, and each R^8 is independently $-SO_2CH_3$, $-SO_2-iPr$, $-SO_2NH-iPr$, $-SONH-nPr$, $-SO_2NEt_2$, $-P(O)(CH_3)_2$, $-P(O)(Et)_2$, $-P(O)(Pr)_2$, Me, OMe, $-O-iPr$, $-OCF_3$, CN, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, or $-C(O)NH-iPr$.

50. The compound of any of claim 42-45 or 47 in which the para R^a is or contains $-P(O)(R^3)_2$ or is one of the following:

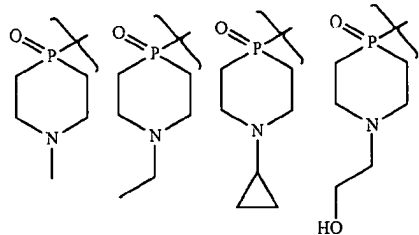
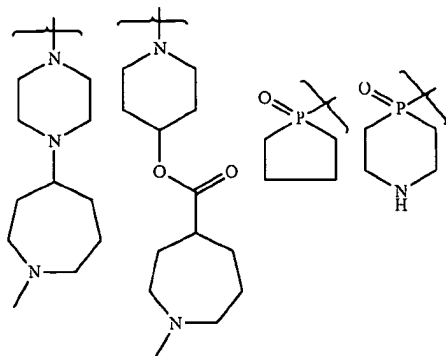
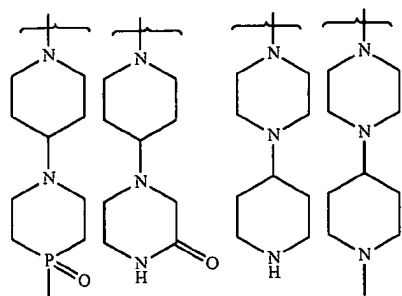
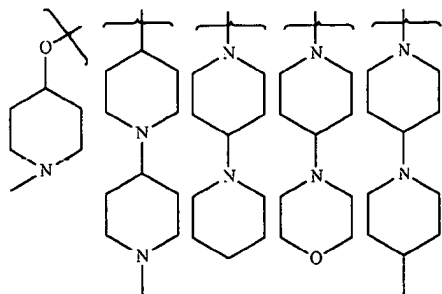
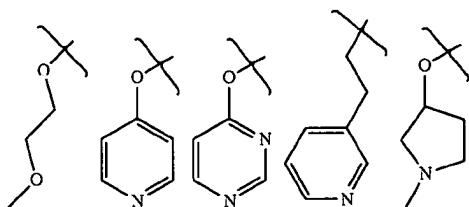


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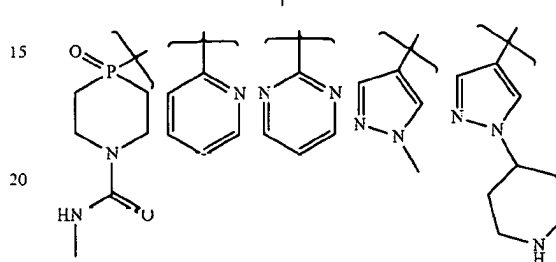
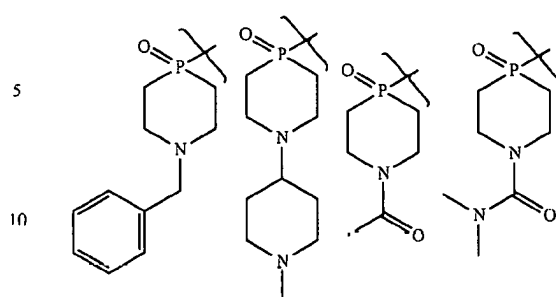
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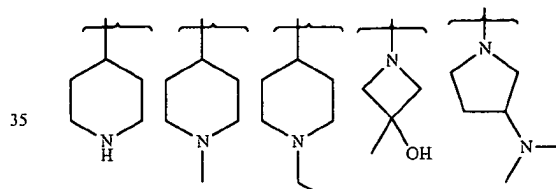
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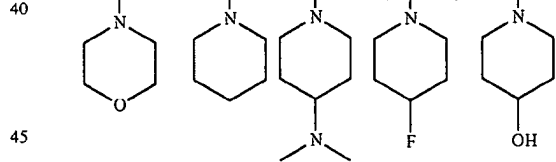
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51. The compound of any of claim 42-45 or 47 in which at least one R^8 is or contains $-P(O)(R^3)_2$ and the para R^a one of the following:

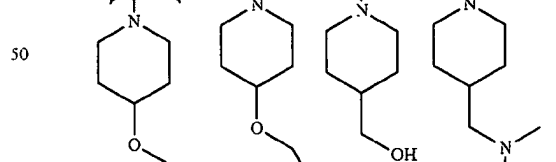
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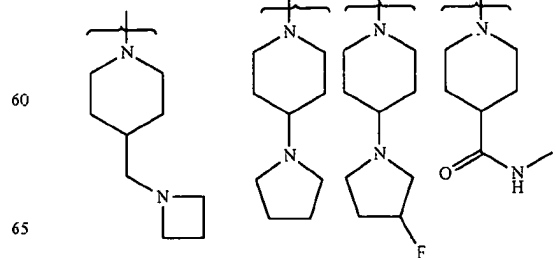
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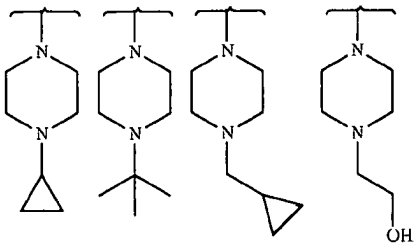
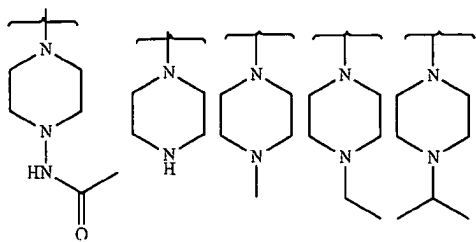
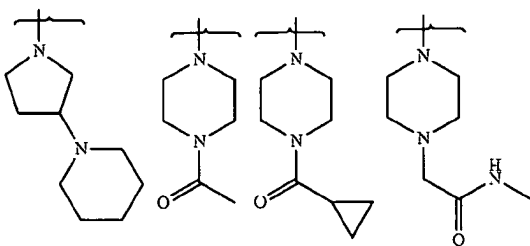
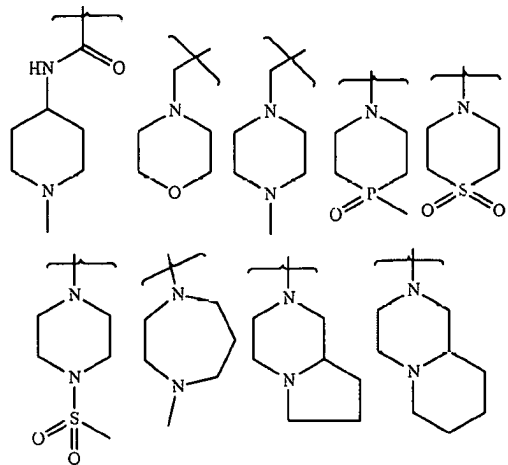
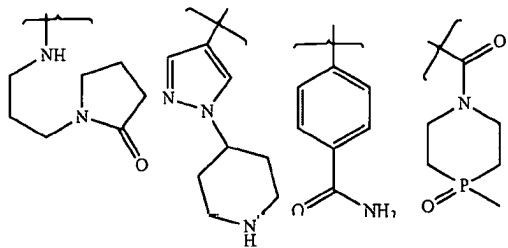


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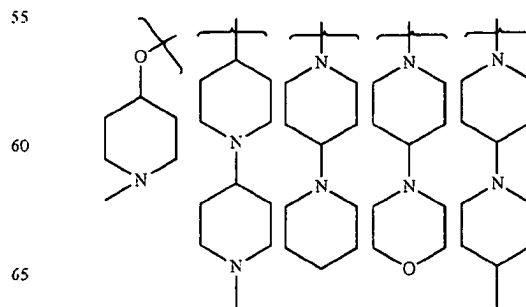
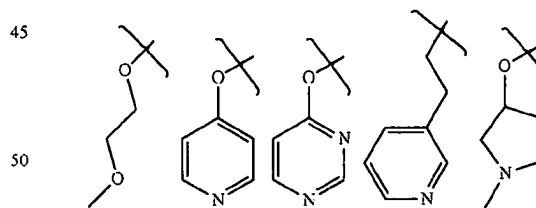
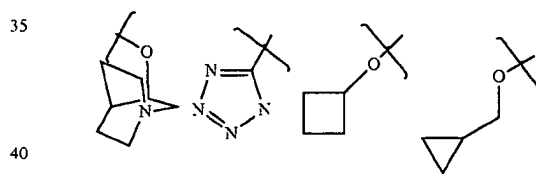
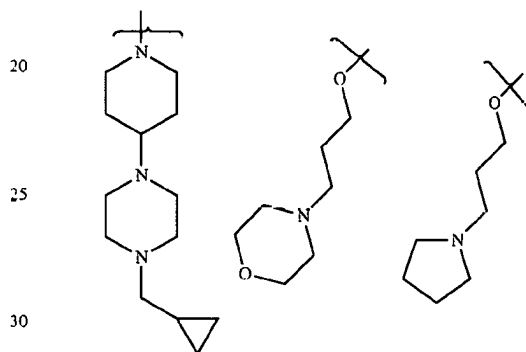
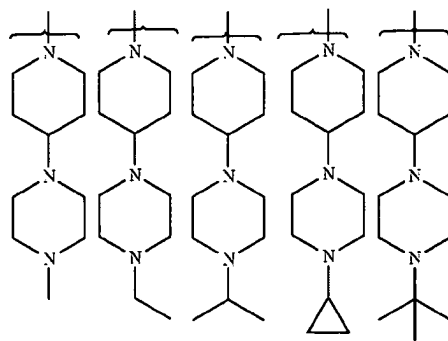
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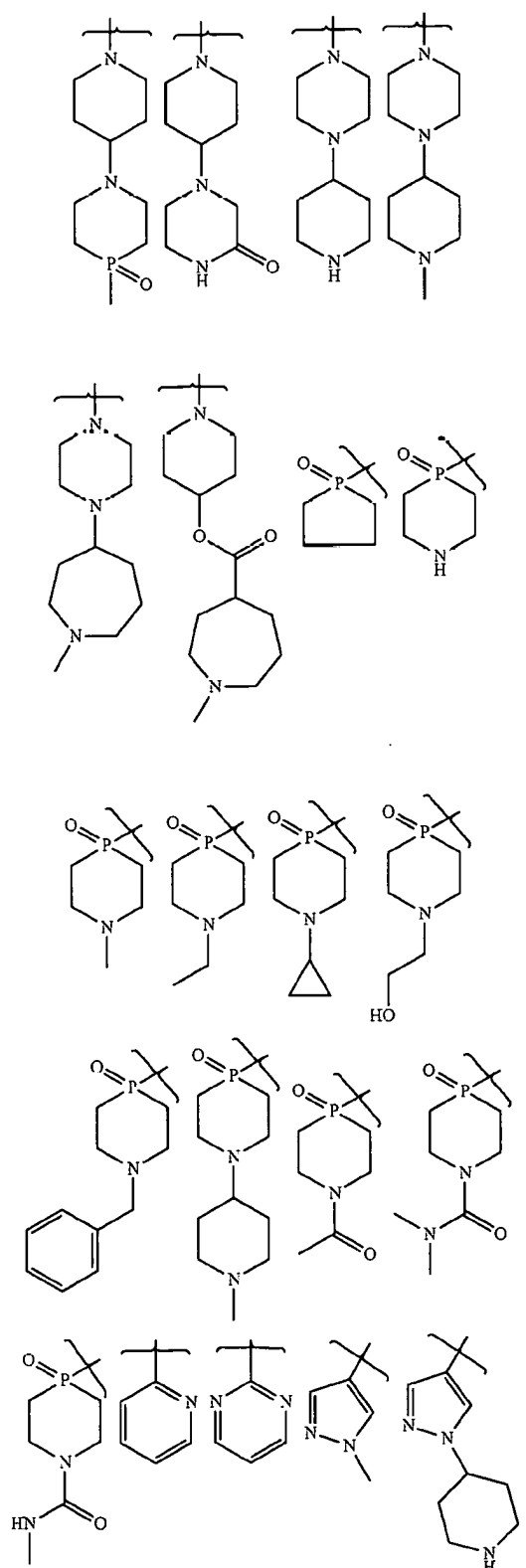
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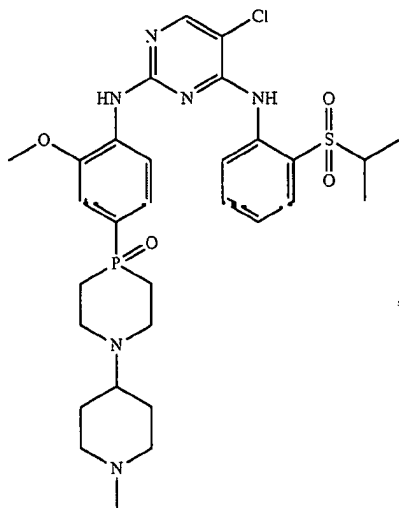


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52. The compound of any of claims 1, 2, 3-7, 8 and 9-33 in which L is NH, Ring E is aryl, and each R⁸ is independently selected from halo, R¹, OR², S(O)_nR² and P(=O)(R³)₂.
53. The compound of claim 52 in which Ring E contains at least one R⁸ in the ortho position, relative to the ring atom attached to L.
54. The compound of claim 52 in which Ring E contains at least one R⁸ in the meta position, relative to the ring atom attached to L.
55. The compound of claim 52 in which Ring E contains at least one R⁸ in the para position, relative to the ring atom attached to L.
56. The compound of claim 52 in which at least one R⁸ is P(=O)(R³)₂, and is —P(=O)(CH₃)₂ or P(=O)(CH₂CH₃)₂.
57. The compound of claim 24 in which L is NH; X¹ is N; X³ is CR⁴; X⁴ is CR⁵; Ring A is aryl and optionally contains up to two additional R⁶; and Ring E is aryl and contains 1-3R⁸, one of which being an ortho, meta or para —P(=O)(R³)₂.
58. The compound of claim 53 in which the at least one R⁸ is —P(=O)(R³)₂ and R³ is —CH₃ or —CH₂CH₃.
59. The compound of claim 54 in which the at least one R⁸ is —P(=O)(R³)₂ and R³ is —CH₃ or —CH₂CH₃.
60. The compound of claim 55 in which the at least one R⁸ is —P(=O)(R³)₂ and R³ is —CH₃ or —CH₂CH₃.
61. A pharmaceutical composition containing a compound of claim 52 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.
62. A pharmaceutical composition containing a compound of claim 56 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.
63. A pharmaceutical composition containing a compound of claim 58 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.
64. A pharmaceutical composition containing a compound of claim 59 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.
65. A pharmaceutical composition containing a compound of claim 60 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.
66. A pharmaceutical composition containing a compound of any of claim 1, 2, 3-7, 8, 9-23 or 38-41, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

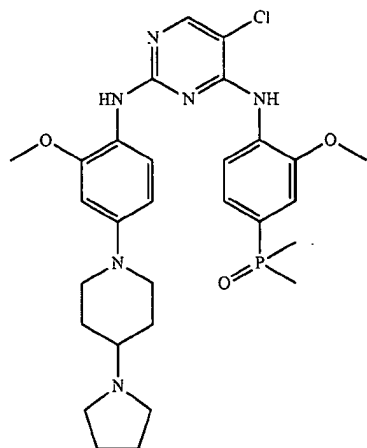
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67. The compound of claim 59, wherein the compound is



or a pharmaceutically acceptable salt thereof.

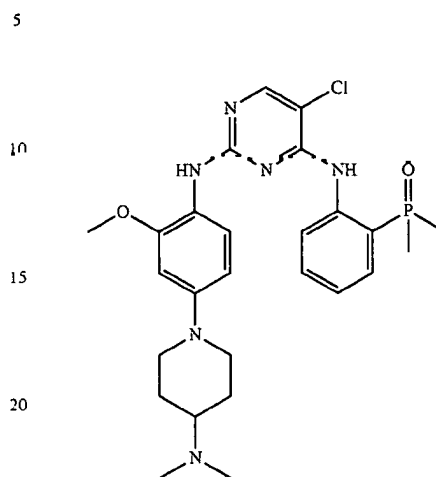
68. The compound of claim 38, wherein the compound is



or a pharmaceutically acceptable salt thereof.

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69. The compound of claim 38, wherein the compound is



or a pharmaceutically acceptable salt thereof.

70. The compound of claim 40, wherein the compound is 5-chloro-N⁴-[4-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

71. The compound of claim 40, wherein the compound is 5-chloro-N²-[6-(dimethylphosphoryl)-2-methoxypyridin-3-yl]-N⁴-[4-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

72. The compound of claim 40, wherein the compound is 5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

* * * * *

EXHIBIT F



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/736,910	01/17/2012	Yihan Wang	11932.0011-00000	5957
104776	7590	02/22/2017		
Ariad/Tinnegan 901 New York Ave NW Washington, DC 20001			EXAMINER CHENG, KAREN	
			ART UNIT 1626	PAPER NUMBER
			NOTIFICATION DATE 02/22/2017	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

regional-desk@finnegan.com



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In re Patent No. 9,012,462 :
Wang et al. : REDETERMINATION OF
Issue Date: April 21, 2015 : PATENT TERM ADJUSTMENT
Application No. 12/736,910 :
Filing or 371(c) Date: January 17, 2012 :
Attorney Docket No. 11932.0011-00000 :

This is in response to patentee's "REQUEST FOR RECONSIDERATION OF DECISION OF REDETERMINATION OF PATENT TERM ADJUSTMENT – POST-GRANT" filed September 22, 2016, requesting the Office change the patent term adjustment determination (PTA) to 591 days.

The Office has re-determined the PTA to be **626** days.

This redetermination of patent term adjustment is NOT the Director's decision on the patentee's request for reconsideration for purposes of seeking judicial review under 35 U.S.C. § 154(b)(4).

Relevant Procedural History

On April 21, 2015, this patent issued with a PTA in the amount of 752 days. On Monday, June 22, 2015, patentee filed a timely request for redetermination of patent term adjustment. On February 24, 2016, the Office mailed a decision correcting the PTA to 436 days. On September 22, 2016, patentee filed the present request for reconsideration, accompanied by a request for a five-month extension of time and fee. Patentee seeks PTA in the amount of 591 days. Specifically, patentee disagrees with the Office assessment of 190 days of applicant delay pursuant to 37 CFR 1.704(c)(7). Patentee asserts that the Office should have entered a period of reduction of 35 days under 37 CFR 1.704(b) (instead of 190 days under 37 CFR 1.704(c)(7)) for the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012.

Redetermination

The Office finds that patentee is entitled to **626** days of PTA.

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As to the amount of applicant delay, the Office concludes that the USPTO assessed the 190-day period of reduction under 37 CFR 1.704(c)(7) in error. Furthermore, the Office finds that an assessment of 35 days of applicant delay as suggested by patentee is not warranted. Accordingly, the Office has removed the period of reduction of 190 days.

The Office finds that the amount of applicant delay is 261 (126 + 32 + 88 + 15) days.

Overall PTA Calculation

Formula:

“A” delay + “B” delay + “C” delay - Overlap - applicant delay = X

USPTO’s Calculation:

$$439 + 448 + 0 - 0 - 261 = 626$$

Patentee’s Calculation

$$439 + 448 + 0 - 0 - 296 = 591$$

Conclusion

Patentee is entitled to PTA of six hundred twenty-six (626) days. Using the formula “A” delay + “B” delay + “C” delay - overlap - applicant delay = X, the amount of PTA is calculated as following: $439 + 448 + 0 - 0 - 261 = 626$ days.

If patentee continues to disagree with the Office’s redetermination of patent term adjustment, patentee has two (2) months from the date of this redetermination to request reconsideration of the patent term adjustment without paying any additional petition fee. This two-month period is extendable under 37 CFR 1.136(a). However, if patentee responds more than two months after the mail date of the redetermination, patentee is required to pay the extension of time fee. After the period to respond has expired, the Office will *sua sponte* issue a certificate of correction adjusting the PTA to six hundred twenty-six (626) days.

Application/Control Number: 12/736,910

Page 3

Art Unit: OPET

Telephone inquiries specific to this matter should be directed to the undersigned at (571) 272-3211.

/Christina Tartera Donnell/

Christina Tartera Donnell
Attorney Advisor
Office of Petitions

Enclosures: Adjusted PTA calculation
 Draft Certificate of Correction

EXHIBIT G

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Wang <i>et al.</i>	Confirmation No.:	5957
Patent No.:	9,012,462	Issued on:	April 21, 2015
Application No.:	12/736,910	Art Unit:	1626
Filing or 371(c):	January 17, 2012	Examiner:	Cheng, Karen
For:	PHOSPHORUS DERIVATIVES AS KINASE INHIBITORS	Attorney Docket No.:	13396-020-999 (previous 11932.0011-00000) CAM: 209362-999020

**REQUEST FOR RECONSIDERATION OF
DECISION OF REDETERMINATION OF PATENT TERM ADJUSTMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Patentee hereby requests reconsideration of the Office's decision of Redetermination of Patent Term Adjustment mailed February 22, 2017, and issuance of a revised determination of patent term adjustment along with a corresponding certificate of correction to correct the patent term adjustment in accordance with the remarks provided herein. Applicants request a two (2) month extension of time from April 22, 2017 to June 22, 2017 for filing a request for reconsideration. Accordingly, this request is timely filed.

The Office has re-determined the patent term adjustment (PTA) to be 626 days. For the reasons set forth below, Patentee respectfully submits that the correct PTA is **591 days**.

I. Relevant Procedural History and Statement of the Facts

U.S. Patent No. 9,012,462 ("the '462 patent") was granted by the U.S. Patent and Trademark Office ("the Office") on April 21, 2015, with a calculated PTA under 35 U.S.C. § 154(b) of 752 days. Patentee filed an Application for Patent Term Adjustment pursuant to 37 C.F.R. § 1.705(b) on June 22, 2015, requesting a redetermination of the PTA to 596 days. In response, the Office mailed a Decision of Redetermination of Patent Term Adjustment ("First PTA Decision") on February 24, 2016, re-determining the PTA to be 436 days.

Patentee then filed a Request for Reconsideration of Decision of Reconsideration of Patent Term Adjustment on September 22, 2016, requesting a redetermination of the PTA to 591 days. In response, the Office mailed a Decision of Redetermination of Patent Term Adjustment (“Second PTA Decision”) on February 22, 2017, re-determining the PTA to be 626 days.¹

II. Calculation of Patent Term Adjustment

With the exception of the Office’s calculation of applicant delay associated with the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012, and thus its calculation of the total PTA, Patentee agrees with the Office’s calculations set forth in the Decision. Specifically, Patentee agrees with the Office’s determinations that:

- the period of A delay is 439 days. Second PTA Decision, page 2.
- the period of B delay is 448 days. *Id.*
- the period of C delay is 0 days. *Id.*
- the period of Overlap is 0 days. *Id.*

Additionally, Patentee agrees with the Office’s determination of applicant delay as follows:

- 126 days of applicant delay related to the filing of the response to Notification of Missing Requirements (beginning on March 8, 2011 and ending on July 11, 2011). Second PTA Decision, page 2; *see also* First PTA Decision, page 5.
- 32 days of applicant delay related to the filing of the response to non-final Office Action (beginning on December 21, 2013 and ending on January 21, 2014). Second PTA Decision, page 2.
- 88 days of applicant delay related to the filing of Request for Continued Examination and response to final Office Action (beginning on June 24, 2014 and ending on September 19, 2014). Second PTA Decision, page 2; *see also* First PTA Decision, page 6.

¹ A Certificate of Correction was issued on June 6, 2017, stating that the PTA for the subject patent is 436 days. It appears that the Certificate of Correction was mistakenly issued by the Office based on the First PTA Decision. As of filing of this request, the current PTA, as shown under the Patent Term Adjustment tab in the Patent Applicant Information Retrieval (PAIR) system, remains as 626 days.

- 15 days of applicant delay related to the filing of 37 C.F.R. § 1.312 amendment after Notice of Allowance (beginning on February 23, 2015 and ending on March 9, 2015). Second PTA Decision, page 2.

The only remaining dispute between Patentee and the Office is the number of PTA days, if any, related to the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012.

The relevant portion of the prosecution history for this request is summarized as follows:

Patentee and the Office are now in agreement that the commencement date is Monday, **November 22, 2010**.

A Notification of Missing Requirements under 35 U.S.C. 371 was mailed by the Office on December 6, 2010. Patentee and the Office are now in agreement that the deadline for Applicant to file a response without incurring applicant delay was Monday, March 7, 2011. A response to the Notification and a Petition under 37 C.F.R. § 1.47(a) were mailed by Applicant on July 6, 2011 and received by the Office on **July 11, 2011**.

The Office mailed a Decision dismissing Applicant's Petition under 37 C.F.R. § 1.47(a) on **September 13, 2011** as lacking an item necessary to grant the petition. The Office set a two-month period (extendable under 37 C.F.R. § 1.136(a)) for Applicant to file a response to request reconsideration on the merits of the petition. Decision of September 13, 2011, page 2.

A Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) was filed by Applicant on **January 17, 2012**.

The Office mailed a Decision granting Applicant's Petition under 37 C.F.R. § 1.47(a) on April 12, 2012.

In the Request for Reconsideration of Decision of Reconsideration of Patent Term Adjustment filed September 22, 2016, Patentee submitted that there are 35 days of applicant delay related to the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012.

In response, the Office considers that the 35 days of applicant delay suggested by the Patentee “is not warranted”. Second PTA Decision, page 2. No further explanation is provided by the Office. Patentee respectfully disagrees and reiterates that there are 35 days of applicant delay under 37 C.F.R. § 1.704(b), which provides:

With respect to the grounds for adjustment set forth in §§ 1.702(a) through (e), and in particular the ground of adjustment set forth in § 1.702(b), an applicant shall be deemed to have failed to engage in reasonable efforts to conclude processing or examination of an application for the cumulative total of any periods of time in excess of three months that are taken to reply to any notice or action by the Office making any rejection, objection, argument, or other request, measuring such three-month period from the date the notice or action was mailed or given to the applicant, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date that is three months after the date of mailing or transmission of the Office communication notifying the applicant of the rejection, objection, argument, or other request and ending on the date the reply was filed. The period, or shortened statutory period, for reply that is set in the Office action or notice has no effect on the three-month period set forth in this paragraph.

37 C.F.R. § 1.704(b) (emphasis added). *See also*, MPEP § 2732 (“The three-month period in 37 CFR 1.704(b) applies to the Office notices and letters issued as part of the pre-examination processing of an application.”).

In the Decision of September 13, 2011, after reviewing Applicant’s Petition under 37 C.F.R. § 1.47(a) and its supporting documents, the Office dismissed the petition based on the reasoning that “[i]t is not clear that the inventors have been presented with a complete copy of the application papers, including the declaration” and that “[f]urther, it does not appear that Mr. Bernstein has firsthand knowledge of points six and seven from the statement of facts.” Decision of September 13, 2011, pages 1–2. Patentee respectfully submits that the Decision of September 13, 2011 is a “rejection” or “objection” to Applicant’s Petition under 37 C.F.R. § 1.47(a) and the Office’s reasoning is an “argument” within the meaning of 37 C.F.R. § 1.704(b).

Moreover, the Office set a two-month period (extendable under 37 C.F.R. § 1.136(a)) for Applicant to file a response. Decision of September 13, 2011, page 2. Patentee respectfully submits that the Decision of September 13, 2011 is also a “request” within the meaning of 37 C.F.R. § 1.704(b).

Accordingly, Patentee respectfully submits that C.F.R. § 1.704(b) is applicable to a response to the Decision of September 13, 2011.

The three-month date to respond to the Decision of September 13, 2011 was **December 13, 2011**. A response—the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a)—was filed on **January 17, 2012**. Accordingly, Patentee respectfully submits that there are 35 days of applicant delay under 37 C.F.R. § 1.704(b) beginning on December 14, 2011 and ending on January 17, 2012.

III. Overall Patent Term Adjustment Calculation

The overall applicant delay:

$$126 + 35 + 32 + 88 + 15 = 296$$

The overall PTA:

$$\begin{aligned} & \text{A delay} + \text{B delay} + \text{C delay} - \text{Overlap} - \text{applicant delay} \\ &= 439 + 448 + 0 - 0 - 296 \\ &= 591 \end{aligned}$$

Therefore, Patentee respectfully submits that the correct patent term adjustment under 35 U.S.C. § 154(b) is **591 days**.

IV. Conclusion

Reconsideration of the Decision and correction of the Patent Term Adjustment calculation are respectfully requested.

An extension of time fee of \$600 for a period of two months is believed to be due for the submission of this paper. The fees will be paid via EFS Web. If any other fees are deemed necessary for the submission of this paper, the Director is authorized to charge the required fees to Jones Day Deposit Account No. 50-3013 (Ref.: 209362-999020).

Respectfully submitted,

Date: June 20, 2017

/Kunyong Yang/

Kunyong Yang

Reg. No. 64,629

For: Dale Rieger

Reg. No. 43,045

JONES DAY

250 Vesey Street

New York, New York 10281-1047

(858) 314-1200

EXHIBIT H

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,012,462 B2
APPLICATION NO. : 12/736910
DATED : April 21, 2015
INVENTOR(S) : Wang et al.

Page 1 of 1

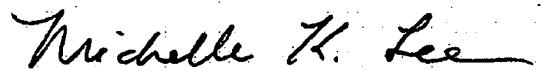
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 436 days.

Signed and Sealed this
Sixth Day of June, 2017



Michelle K. Lee
Director of the United States Patent and Trademark Office

EXHIBIT I



United States Patent and Trademark Office

Office of the Commissioner for Patents

PHOSPHORUS DERIVATIVES AS KINASE INHIBITORS

PATENT # 9012462 APPLICATION # 12736910 FILING DATE 01/17/2012 ISSUE DATE 04/21/2015

Payment Window Status

WINDOW STATUS FEES
3.5 Year Not Open Not Due

No maintenance fees are due at this time. 3.5 year window opens on 04/21/2018.

Window	First Day to Pay	Surcharge Starts	Last Day to Pay	Status	Fees
3.5 Year	04/21/2018	10/23/2018	04/22/2019	Not Open	Not Due
7.5 Year	04/21/2022	10/22/2022	04/21/2023	Not Open	Not Due
11.5 Year	04/21/2026	10/22/2026	04/21/2027	Not Open	Not Due

Patent Holder Information

Customer # 147272
Entity Status SMALL
Phone Number 2123263939
Address Jones Day for Takeda
250 Vesey Street
New York, NY 10281-1047
UNITED STATES

EXHIBIT J

Chronological Summary of Regulatory Activities for ALUNBRIG Approval

Contact Date	Title
February 28, 2011	Request for Type B pre-IND meeting (Sequence# 0000)
March 11, 2011	Email from FDA granting pre-IND meeting (date 2011-05-24)
April 21, 2011	Original Type B pre-IND meeting briefing book for 2011-05-24 (SN# 0001)
May 24, 2011	Official FDA meeting minutes from pre-IND meeting held 2011-05-24
June 28, 2011	Original IND Submission (IND 110935, SN# 0002) Includes Protocol AP26113-11-101 (version 1 dated 2011-06-27)
July 20, 2011	Comments and Clinical deficiency letter from FDA Clinical reviewer. 1. Indicate in protocol that for purposes of dose escalation and dose modification, "drug-related" toxicities will include any toxicity that is possibly, probably, or definitely drug-related. 2. State rationale for concomitant med prohibition and include a list of such medications. 3. Provide a copy of the Consent Form.
July 20, 2011	FDA's comments on Clinical Pharmacology section of IND application 1. Add a specific warning in the Concomitant Medication Section for use of potent CYP2C8 substrates and inhibitors 2. Evaluate the food effect on the pharmacokinetics of AP26113 as early as possible during drug development to adequately inform selection of the dosage regimen with regard to food.
July 20, 2011	FDA CMC comments and request for additional information - drug substance; drug product questions
July 21, 2011	FDA CMC Deficiency Comments - ARIAD requested comments resent as they were sent to the wrong email address
July 22, 2011	ARIAD's initial response to clinical deficiencies in IND submission
July 24, 2011	Initial response to 2011-07-20 CMC deficiency letter
July 25, 2011	ARIAD response to Clinical deficiencies, including AP26113-11-101 protocol amendment 1 (SN# 0004)
July 25, 2011	Full response to 2011-07-20 CMC deficiency letter (SN# 0003)
July 26, 2011	FDA "safe to proceed" letter for IND 110935 - one CMC comment
September 8, 2011	ARIAD response to five 2011-07-20 CMC questions and comments - Lot CoA (SN# 0005)
December 14, 2012	Request for Fast Track designation
January 11, 2013	Request for Type B End-of-Phase 1 meeting
January 15, 2013	EOP1 FDA Meeting Request Granted - scheduled for 2013-03-18
February 12, 2013	Denial of 2012-12-14 application for Fast Track designation - not demonstrated that an unmet medical need exists for patients who have not received crizotinib (i.e., crizotinib-naïve patients) and the request does not contain a description of the drug development plan.
February 15, 2013	Briefing Package for Type B End-of-Phase 1 meeting to be held 2013-03-18 (SN# 0043)
March 11, 2013	Preliminary Comments on 2013-03-18 Type B End-of-Phase 1 meeting package sent 2013-02-15
March 28, 2013	Final meeting minutes from 2013-03-18 End of Phase 1 meeting
May 31, 2013	Breakthrough Therapy Designation Request - patients with ALK+ metastatic small cell lung cancer resistant to crizotinib (SN# 0053)
May 31, 2013	Updated data from Protocol AP26113-11-101 - enrollment in the Phase 2 expansion cohort per Q5 of Pre-IND Meeting Minutes (SN# 0054)
July 11, 2013	Information Request for Breakthrough Therapy Designation: : Please clarify the numbers of ALK positive NSCLC patients with: 1. Confirmed responses 2. Number of patients treated at recommended dose
July 12, 2013	Response to Information Request for Breakthrough Therapy Designation
July 18, 2013	Response to Information Request for Breakthrough Therapy Designation Request
July 18, 2013	Information Request for Breakthrough Designation Request – Clinical - clarify that 1/13 confirmed responses was in Crizotinib naïve patient (aCR) and

Contact Date	Title
	2. Of the 7 unconfirmed responses, 3 patients in PR are awaiting a confirmatory scan, 3 lost the response (as per briefing document), please update RR of 1 patient
July 19, 2013	Responses to FDA Requests for Information Regarding Breakthrough Designation (SN# 0060)
July 29, 2013	Denial of 2013-05-31 application for Breakthrough Therapy Designation - the preliminary clinical evidence you submitted does not indicate that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. May submit a new request if you see evidence of a high confirmed objective response rate with long duration of response in a larger number of patients.
July 29, 2013	Breakthrough Therapy Designation Denied Letter
August 22, 2013	Type B Meeting Request US (EOP2) (SN# 0063)
August 30, 2013	Approval of ARIAD Type B Meeting request to discuss Phase 3 randomized trial - date set for 2013-10-24
September 24, 2013	Submission of Type B Meeting briefing book per 2013-08-30 FDA request (SN# 0066)
October 22, 2013	FDA Meeting Preliminary Comments related to 2013-10-24 Type B meeting
October 23, 2013	Withdrawal of request for 2013-10-26 Type B meeting, originally requested in SN# 0063 (SN# 0068)
October 23, 2013	Email from FDA requesting to discuss development of the "Master Protocol" Concept in place of cancelled 2013-10-24 Type B meeting
October 23, 2013	Response to 2012-10-22 FDA draft responses and comments regarding 2013-10-24 Type B meeting
October 24, 2013	FDA amendments to its 2013-10-22 preliminary response to ARIAD Type B Meeting package. Specifically FDA withdraws its "Additional Clinical Pharmacology" comments 11 and 17, and provides its reasons.
June 4, 2014	FDA response to 2014-05-29 request for feedback on proposed Breakthrough Therapy designation request. FDA clarification of the additional data and the baseline features that will be important and support the BTDR package
August 11, 2014	Breakthrough Therapy Designation Request - 11 August 2014 resubmission of a new Breakthrough Therapy (BT) request for the treatment of patients with ALK+ NSCLC that is resistant or intolerant to crizotinib (SN# 0101)
September 10, 2014	Information Request and clinical comments regarding 2014-08-11 Breakthrough Designation Request - response due 2014-09-12 1. Provide ARIAD's general investigation plan for AP26113. 2. Of the patients with ALK+ NSCLC who developed resistance or intolerance to crizotinib, describe the percentage of patients in each category and definitions of resistance and intolerance. 3. Describe how NSCLC patients were selected for ALK positivity (ie test used). 4. Clarify the definition of a "confirmed response."
September 15, 2014	Response to 2014-09-10 FDA Information Request regarding the 2014-08-11 Breakthrough Designation Request (SN# 0104)
October 1, 2014	Breakthrough Therapy Designation Granted
March 13, 2015	Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting Request for the week of 2015-05-11
March 25, 2015	Breakthrough Therapy Meeting granted - date of 2015-06-30
May 18, 2015	Clinical Pharmacology and Statistics - ECG Cardiac Safety Report - Request for QT-IRT Review by end of July 2015 (SN# 0143)
May 21, 2015	ALK Inhibitors Master Protocol - National Cancer Institute request for Pre-IND/End-of-Phase 2 Meeting and pre-IND number
June 1, 2015	Briefing Book for Type B Breakthrough meeting scheduled for 2015-06-30 (SN# 0147)
June 12, 2015	ALK Inhibitors Master Protocol to PIND 126676 - Meeting package for NIH-NCI Pre-IND/EOP2 meeting scheduled for 2015-07-10

Contact Date	Title
June 22, 2015	Request for additional ECG datasets for Study AP26113-11-101 - requested by FDA for their review of Sequence 0143 dated 2015-05-18
June 24, 2015	Response to 2015-06-22 request for additional ECG datasets for Study AP26113-11-101 (SN# 0153)
June 30, 2015	Preliminary comments on 2015-03-13 request for Type B comprehensive, multidisciplinary breakthrough therapy meeting
June 30, 2015	FDA Advice and Information Request regarding ECG dataset from Study AP26113-11-101 - resubmit the ecg dataset with updated treatment group and dosing information
July 6, 2015	Response to 2015-06-30 Information Request - AP26113-11-101 revised dataset ADEGEXD.xpt for the QT/IRI review (SN# 0157)
July 14, 2015	FDA request for earlier submission of ECG Waveform data - Study AP26113-11-101
July 15, 2015	Email response to 2015-07-14 request for revised submission timeline for ECG Waveform data - AP26113-11-101
July 22, 2015	Official minutes of the Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy meeting held 2015-06-30
August 4, 2015	Type B CMC Meeting Request - Breakthrough Therapy (SN# 0162)
August 17, 2015	FDA notification that Type B CMC meeting will be granted as a teleconference on 2015-09-25
August 24, 2015	Email response to 2015-06-22 request for ECG Waveform data for AP26113-11-101 - Vendor final notice of completed data upload
August 25, 2015	Initial Pediatric Study Plan (iPSP) dated 2015-08-21 - request a waiver from brigatinib from PREA (SN# 0167)
August 27, 2015	Briefing Package for Type B CMC Breakthrough Therapy Meeting scheduled for 2015-09-25 (SN# 0168)
August 28, 2015	Request for Proprietary Name Review: ALUNBRIG (SN# 0169)
September 15, 2015	Type B CMC Meeting scheduled for 2015-09-25 - Meeting Preliminary Comments received from FDA
September 17, 2015	FDA Request for Information - request for list of authorized sponsor contacts for IND 110935 - reply by 2015-09-23
September 21, 2015	Request cancellation of Type B CMC Meeting scheduled for 2015-09-25
October 6, 2015	Written Response to FDA Pre-Meeting Comments - Type B CMC Meeting - 25 September 2015 (SN# 0175)
October 6, 2015	NDA 208772 for brigatinib (AP26113) - pre-assigned NDA number
October 12, 2015	Type B CMC Meeting Request - second CMC meeting (SN# 0177)
October 15, 2015	Type B CMC Meeting Request Granted Letter - second CMC meeting - scheduled for 2015-12-07
October 19, 2015	Request for Feedback: Case Definition of Early Onset Pulmonary Events submitted in response to Type B mtg held 2015-06-30 (SN# 0178)
October 30, 2015	FDA Advice Letter regarding pulmonary events case review and proposed case definition submitted 2015-10-19 - assess for the overall incidence of pneumonitis based on a separate case definition encompassing all pneumonitis events (as described in criteria 2) but excluding criteria 1 ("Presence of a temporal relationship.....").
November 4, 2015	Type B CMC Meeting scheduled for 2015-12-07 - Second CMC meeting - Briefing Book (SN# 0182)
November 5, 2015	FDA advice letter - FDA clarification on ARIAD response plan - Two analyses of pulmonary events requested
November 12, 2015	New Protocol AP26113-13-301 version 1 dated 2015-10-22 ; Request for FDA Feedback (SN# 0185)
November 13, 2015	Written Response to Initial Pediatric Study Plan (iPSP) dated 2015-08-21 (Sequence 0167) - Agreed iPSP requested
November 16, 2015	Proprietary Name Request Conditionally Acceptable - Alunbrig

Contact Date	Title
November 24, 2015	Revised written response to 2015-09-15 FDA Pre-meeting Comments on Type B CMC Meeting - feedback requested (SN# 0188)
December 4, 2015	Type B CMC Meeting scheduled for 2015-12-07 - Slide Deck in pdf format to facilitate discussion
December 10, 2015	Type B CMC Meeting held on 2015-12-07 - Official FDA meeting minutes
December 16, 2015	ECG waveform data for IND 110935 - Request FDA review status of data available to FDA reviewer as of 2015-08-24
December 17, 2015	FDA Advice - Information Request - Response to ARIAD request for clarification dated 2015-11-24 (Sequence 0188)
December 17, 2015	ECG waveform data for IND 110935 - FDA response to 2015-12-16 review status request
January 5, 2016	Meeting Request - Type B Pre-NDA CMC-specific Meeting Request (SN# 0195)
January 8, 2016	Response to FDA comment dated 2016-01-05 regarding AP26113-13-301 protocol synopsis in Sequence 0185 dated 2015-11-12. A copy of response was sent via email on 2016-01-05. (SN# 0196)
January 21, 2016	FDA Advice - Information Request - Response to questions submitted in SN# 0185 dated 2015-11-12 - clinical and statistical comments and recommendations regarding Protocol AP26113-13-301
January 21, 2016	Type B Pre-NDA CMC-specific Meeting Request Granted - scheduled for 2016-03-02
January 29, 2016	Briefing materials for Brigatinib - Type B CMC-specific Pre-NDA meeting scheduled for 2016-03-02. (SN# 0198)
February 5, 2016	Submission of agreed Initial Pediatric Study Plan (iPSP) to IND 110935 for Brigatinib. (SN# 0200)
February 12, 2016	Type B Interdisciplinary Pre-NDA Meeting Request (SN# 0201)
February 22, 2016	Email from ARIAD to clarify questions on 2016-02-22 FDA Advice-Information letter on AP26113-11-101 ECG data - ECG warehouse data
February 22, 2016	FDA Advice and Information Request regarding ECG assessment of Study AP26113-11-101
February 24, 2016	Meeting Preliminary Comments for the Type B Pre-NDA CMC Only meeting scheduled for 2016-03-02
February 24, 2016	Type B Interdisciplinary Pre-NDA Meeting granted and scheduled for 2016-04-15
February 24, 2016	FDA response to 2016-02-22 ARIAD questions in follow-up to 2016-02-22 FDA Advice-Information letter on ECG data
February 29, 2016	Response to FDA Advice - Information Request dated 2016-01-21 regarding AP26113-13-301 (SN# 0204)
March 7, 2016	Agreed Initial Pediatric Study Plan (iPSP) for Brigatinib - ARIAD acceptance of Agreed iPSP dated 2016-03-07
March 7, 2016	FDA comments on agreed Initial Pediatric Study Plan (iPSP) for Brigatinib
March 8, 2016	Official FDA meeting minutes from Type B pre-NDA CMC only Meeting held 2016-03-02
March 10, 2016	Response to 2015-10-30 FDA Advice and Information Request - Pulmonary AE Case Review (SN# 0207)
March 16, 2016	Type B Interdisciplinary Pre-NDA Meeting scheduled for 2016-04-15 - Meeting Package and 20 Desk Copies.
March 18, 2016	Updated top-line data from ALTA - ARIAD planned submissions to FDA prior to pre-NDA meeting scheduled for 2016-04-15
March 29, 2016	FDA agreement with 2016-02-29 Response to Information Request dated 2016-01-21 - regarding the proposed dose and dosage regimen for the confirmatory trial (AP26113-13-301)
April 4, 2016	Clinical: ALTA Top-line Data from 29 February 2016 Data Extraction (SN# 0212)
April 4, 2016	ARIAD written response to 2016-03-08 FDA official minutes of pre-NDA CMC meeting held 2016-03-02 (SN# 0211)
April 8, 2016	FDA unofficial feedback on Sequence 0211 filed 2016-04-04 - Response to ARIAD request for feedback prior to pre-NDA meeting
April 12, 2016	Meeting Preliminary Comments for the Type B Pre-NDA meeting scheduled for 2016-04-15

Contact Date	Title
April 14, 2016	ARIAD response to 2016-04-12 FDA meeting preliminary comments for Type B pre-NDA meeting and request to cancel meeting
April 14, 2016	FDA response to 2016-04-14 request to cancel Type B pre-NDA meeting - Teleconference required for formal capture of agreement
April 14, 2016	Contact Report - ARIAD called RPM at FDA regarding FDA request for teleconference to capture agreement
April 19, 2016	Official FDA meeting minutes from Type B pre-NDA teleconference held 2016-04-15
April 25, 2016	Request for Rolling Submission for NDA 208772 - proposal to submit in three parts - Part 1: Submit by the end of June 2016 to include most of Module 1 documents (excludes risk management plan [RMP] and labeling) and all nonclinical sections. - Part 2: Submit by the end of July 2016, to include the CMC sections. - Part 3: Submit by the end of August 2016, to include all clinical sections including the exposure-response analyses from Study AP 26113-13-201, the RMP, and the labeling (including patient prescribing information.) The content and timing of the 30-day stability [by end of September 2016] and 60-day safety update [by end of October 2016] also is provided.
May 2, 2016	New Protocol AP26113-16-901: Intermediate-sized Expanded Access Protocol (EAP) for brigatinib
May 17, 2016	FDA review status of EAP AP26113-16-901 submitted 2016-05-02 in SN# 0217 - FDA request investigator data and ICF
May 25, 2016	Rolling review request for NDA 208772 for brigatinib granted by FDA
June 3, 2016	Presentation and Posters for ASCO 2016 (AP26113-13-201 (ALTA) and AP26113-11-101)
June 13, 2016	AP26113-13-201 ALTA IRC data requested during pre-NDA meeting held 2016-04-15 (SN# 0228)
June 14, 2016	ALTA IRC data - FDA notification that clinical team has reviewed the information and have no further comments
June 16, 2016	Original NDA for brigatinib - Presubmission to NDA Rolling Submission - Part 1 (Non-clinical) (SN# 0001)
July 28, 2016	Original NDA for brigatinib - Presubmission to NDA Rolling Submission: Part 2 (CMC); Change in contact (SN# 0002)
August 2, 2016	FDA OSI Review Comments and Information Request for revised dataset for AP26113-13-201 and Financial Disclosure Information
August 4, 2016	Response to FDA request dated 2016-08-02 for revised BIMO datasets - AP26113-13-201
August 5, 2016	Response to FDA request dated 2016-08-02 for revised BIMO datasets - AP26113-13-201. Financial disclosure information was submitted in the first portion of the NDA on 2016-06-16 in SN# 0001. A copy of responses was sent via email on 2016-08-04. (SN# 0003)
August 8, 2016	FDA CMC Information Request for updated letter of authorization for DMF 2880
August 9, 2016	Response to FDA request dated 2016-08-08 for updated Letter of Authorization (LOA) for DMF 2880 - Clariant Corporation. A copy of response was sent via email on 2016-08-09. (SN# 0004)
August 29, 2016	Original NDA Submission - Rolling Submission Part 3 (Clinical); Priority Review Designation Request. (SN# 0005)
September 2, 2016	FDA request for signed Form FDA 356h for NDA 208722 Sequences 0001, 0002, 0003, 0004
September 2, 2016	Signed Form FDA 356h for NDA Sequences 0001, 0002, 0003 and 0004 (SN# 0006).
September 9, 2016	Proprietary name request conditionally acceptable - Alunbrig
September 9, 2016	Application Orientation Meeting (AOM) - FDA confirmation of meeting scheduled for 2016-10-21
September 9, 2016	Application Orientation Meeting (AOM) to discuss brigatinib scheduled for 2016-10-21 - Application Orientation Meeting (AOM) is scheduled for 2016-10-21 from 1:00 to 2:20pm. - Datasets Orientation Meeting (DOM) is scheduled for the same day from 2:30 to 3:30pm. Note: This is an Informal Type C Meeting and meeting minutes will not be issued.

Contact Date	Title
September 13, 2016	FDA Clin/Pharm Information Request - Analysis datasets for three reports a. PopPK Analysis of Phase 1 and Phase 2 PK Data b. Analyses of the Relationship between Brigatinib Exposure and Selected Safety and Efficacy Outcomes c. E-R Analyses of Brigatinib in the ALTA study
September 14, 2016	FDA request for authorized contacts at Biomedical Systems
September 15, 2016	Response to 2016-09-14 FDA request ID 3985796 for Biomedical Systems contact information. Response also submitted to FDA by email on 2016-09-14. (SN# 0007)
September 16, 2016	NDA 208772 Amendment 003 - Response to FDA Clinical Pharmacology dated 2016-09-13 for PopPK datasets. Response also submitted to FDA by email on 2016-09-14. (SN# 0008)
September 19, 2016	Inspection - Notice of FDA BIMO inspection in South Korea (Principal Investigator Sang-We Kim at Asan Medical Center, Department of Oncology, Seoul, Korea) planned for 2016-11-07 through 2016-11-11
September 19, 2016	Inspection - Notice of FDA BIMO inspection in South Korea (Principal Investigator Dong-Wan Kim, Seoul National University Hospital, Seoul, Korea) planned for 2016-11-14 through 2016-11-18
September 20, 2016	Response to FDA request dated 2016-05-17 for AP26113-16-901 New Investigator data and Model Informed Consent Form (SN# 0237)
September 27, 2016	Application Orientation Meeting (AOM) to discuss brigatinib rescheduled from 2016-10-21 to 2016-10-18
September 27, 2016	30 Day Additional Stability Data for drug substance and drug product 30 mg and 90 mg (SN# 0009)
September 29, 2016	FDA request for a revised Form FDA 356h for DS manufacturer AMRI Rensselaer Inc.
September 30, 2016	Method Verification Materials for Alunbrig tablets 30 mg and 90 mg Requested
September 30, 2016	Response to FDA request dated 2016-09-30 - Revised Form FDA 356h to include AMRI Rensselaer Inc. (SN# 0010)
October 4, 2016	Response to FDA request dated 2016-09-30 for Method Verification Materials for Alunbrig
October 4, 2016	Inspection - Internal notification - FDA inspector for site 915 has been identified as Byungja Marciante
October 5, 2016	Method Verification Materials received - Follow-up inquiry regarding return of 2 TempTales to ARIAD
October 5, 2016	Response to FDA request dated 2016-09-30 for Method Verification Materials for Alunbrig - Updated info for Shipment 2
October 6, 2016	FDA NDA review Information Request - OSI request regarding AP26113-13-201 ALTA protocol
October 6, 2016	FDA NDA review Information Request - Clinical Pharmacology
October 7, 2016	Response to FDA request dated 2016-10-06 for AP26113-13-201 Summary of Changes (SN# 0011)
October 11, 2016	Application Orientation Meeting (AOM) scheduled for 2016-10-18 - Meeting package and ARIAD attendee list
October 12, 2016	Application Orientation Meeting (AOM) scheduled for 2016-10-18 - Updated ARIAD attendee list
October 13, 2016	FDA Clinical Information Request regarding AP26113-16-901 - 1. Provide a descriptive schedule of laboratory assessments to be performed during the treatment course, including measurement of pancreatic enzymes and creatinine phosphokinase (CPK), at determined intervals (e.g. every 8-12 weeks). 2. Provide a statement within the ICF instructing patients to notify the Investigator of any visual changes experienced during the treatment course. 3. Include a provision within the protocol to discontinue brigatinib for progression events.
October 13, 2016	AP26113-16-901 - designated as a treatment protocol
October 14, 2016	FDA NDA review Information Request – Statistics - provide the SAS codes used to generate the tables and figures in the CSR for AP26113-13-201

Contact Date	Title
October 17, 2016	Application Orientation Meeting (AOM) scheduled for 2016-10-18 - Updated Meeting packages for AOM and DOM
October 19, 2016	FDA NDA review Information Request – Clin Pharm - population PK analysis dataset for brigatinib study AP26113-13-201
October 21, 2016	Response to 2016-10-14 FDA Statistical Review Request for Information - AP26113-13-201 SAS codes. Response was sent via email on 2016-10-19. (SN# 0012)
October 21, 2016	Response to 2016-10-06 FDA Clinical Pharmacology Request for Information - updated population PK datasets. A copy of this response was sent to FDA on 2016-10-20 by email. (SN# 0013)
October 28, 2016	NDA 208772 application for brigatinib is sufficient for substantive review - RFI • CMC request: Resubmit revised primary and secondary labels • Clin-Pharm requests regarding Study AP26116-13-201 • FDA labeling comments
October 28, 2016	NDA 60 Day Safety Update (SN# 0014)
November 3, 2016	Response to FDA clinical pharmacology comments and requests for information dated 2016-10-19 and 2016-10-28. (SN# 0015)
November 4, 2016	FDA NDA review Information Request - CMC
November 7, 2016	Response to FDA Info Request (13Oct2016) - 901 Amendment 1 and Updated ICF (SN# 0248)
November 7, 2016	FDA NDA review Information Request – Clin Pharm - submit the right dataset (nm_pk_26Oct2016.csv) and revise the PPK model to reduce the bias of CWRES-Time plot, and submit the new model.
November 8, 2016	FDA Notice of Inspection - Form FDA 482 - Biomedical Systems Corp Maryland Heights MO
November 9, 2016	FDA NDA review CMC Information Request - Reference is made to Blend Uniformity (BU) test, Content Uniformity (CU) test, Product Performance Qualification (PPQ), in-process control (IPC) results for all primary stability batches manufactured at Xcelience and Penn, microbiology.
November 10, 2016	AP26113-16-901 - Study may proceed letter
November 11, 2016	Teleconference planned for 2016-11-23 to clarify the popPK dataset submitted 2016-11-08
November 11, 2016	Response to 2016-11-07 FDA clinical pharmacology comments and requests for information dated 2016-11-07. (SN# 0016)
November 18, 2016	Response to 2016-10-28 FDA CMC review comments in NDA Filing Communication. A copy of this response was sent to FDA by email on 2016-11-16. (SN# 0018)
November 18, 2016	Response to 2016-11-04 FDA Request for Information – CMC - Revisions to Module 2.3.P, Module 3.2.P.5.1, Module 3.2.P.5.4. (SN# 0017)
November 21, 2016	Response to 2016-10-28 FDA Labeling and CMC comments and RFI in NDA Filing Communication (SN# 0019)
November 22, 2016	Response to FDA CMC Review Comments and Information Request dated 2016-11-09. (SN# 0020)
November 23, 2016	FDA NDA review Information Request – Statistics - Provide executable SAS program(s) to duplicate the analysis datasets.
November 29, 2016	FDA NDA review Information Request - CMC - Drug Substance; Drug Product; Biopharmaceutics; additional requests regarding dissolution data at 20 minutes.
December 5, 2016	Poster Presentation for World Conference on Lung Cancer (WCLC) in Vienna, Austria in December 2016 - updated clinical data from brigatinib phase 2 study AP26113-13-201 (ALTA)
December 7, 2016	Response to NDA statistical review comments and information request dated 2016-11-23 (SN# 0021)
December 8, 2016	FDA NDA review comments and information request - Clinical - provide an analysis of response rate for patients whose best response was disease progression during crizotinib treatment, etc.

Contact Date	Title
December 8, 2016	FDA NDA review comments and information request - CMC - Propose a packaging strategy that allows for pharmacy dispensing of Alunbrig quantities not captured by the currently proposed packaging configurations.
December 8, 2016	FDA inspection of ARIAD regarding Brigatinib NDA held 2016-11-29 through 2016-12-02 - no Form FDA 483 issued
December 12, 2016	FDA NDA review comments and information request - Statistics - discrepancy in datasets submitted 2016-12-07 and datasets submitted 2016-08-29 and clarify how the TM2NXCYC variable was used in the definition of confirmed ORR.
December 13, 2016	FDA clarification of 2016-12-12 additional statistical request for information - Comment 1 withdrawn
December 13, 2016	Response to CMC review comments and information request dated 2016-11-29 (SN# 0022)
December 14, 2016	Response to CMC review comments and information request 4024376 dated 2016-12-08 (SN# 0023)
December 14, 2016	Response to clinical review comments and information request dated 2016-12-08 (SN# 0024)
December 16, 2016	FDA NDA review CMC Information Request 12-16-16 - response due 2017-01-06
December 20, 2016	FDA proposed PMR-PMC - Clinical Pharmacology
December 20, 2016	Response to NDA statistical review comments and information request dated 2016-12-12 (SN# 0025)
December 22, 2016	FDA Request for clinical info on heart rate, existing tables, dosage, toxicity & Arm A/Arm B patient crossover results
December 22, 2016	Request from FDA to develop a timeline to conduct a PMR trial comparing brigatinib to an available therapy in NSCLC patients
January 3, 2017	Mid-Cycle Communication - Official minutes of the teleconference held 2016-12-14 - Update on the review status of NDA 208772
January 3, 2017	FDA NDA review Information Request 1-3-17 - CMC - Provide the duplicate test results for samples BU-4 and BU-5
January 5, 2017	FDA NDA review comments and information request - Clinical – Financial disclosure related requests.
January 5, 2017	Response to 2016-12-16 and 2017-01-03 Requests for Information – CMC (SN# 0027)
January 5, 2017	Response to proposed PMR clinical dated 2016-12-22 (SN# 0026)
January 6, 2017	Response to proposed Clin-Pharm PMR-PMC dated 2016-12-20 (SN# 0029)
January 6, 2017	Response to clinical information request 4032251 dated 2016-12-22 - Corrigendum CSR AP26113-13-201 (SN# 0028)
January 9, 2017	FDA NDA review Information Request – Labeling comments
January 11, 2017	Press Release: Takeda to acquire ARIAD Pharmaceuticals Inc - notification to FDA - filed to IND and NDA for brigatinib
January 11, 2017	Response to clinical review comments and information request 4037340 dated 2017-01-05 (SN# 0030)
January 13, 2017	Type C Meeting Request: IND 110935, Study AP26113-16-202 (SN# 0267)
January 17, 2017	FDA NDA review Information Request - CMC - Module 3 updates
January 19, 2017	Type C Meeting Request granted - Written Responses are appropriate
January 24, 2017	FDA CMC Information Request and Telecon request for 2017-01-25 regarding dissolution acceptance criterion and Module 3 update
January 25, 2017	Response to CMC Request for Information dated 2017-01-17 (SN# 0031)
January 25, 2017	CMC teleconference held 2017-01-25 - ARIAD follow-up proposal on submission strategy and timing of Module 3 updates
January 26, 2017	Response to CMC Request for Information dated 2017-01-24 - Response Part 1 of 3 (SN# 0033)
January 26, 2017	FDA response to proposed change in due date (2017-02-03) for response to dissolution data request

Contact Date	Title
January 27, 2017	FDA request for clinical teleconference (2017-02-01) - Discuss potential new PMC relating to duration of response and intracranial response rate
January 27, 2017	FDA comments on labeling
January 27, 2017	Response to CMC Labeling Request for Information dated 2017-01-09 (SN# 0032)
January 27, 2017	Response to CMC Request for Information dated 2017-01-24 - Response Part 2 of 3 (SN# 0034)
February 2, 2017	Late cycle meeting for NDA 208772 scheduled to occur in person on 2017-02-24
February 2, 2017	Response to CMC Request for Information dated 2017-01-24 - Response Part 3 of 3 (SN# 0035)
February 7, 2017	Clinical teleconference scheduled for 2017-02-09 – discuss clinical RFI dated 2017-02-07
February 7, 2017	FDA NDA review comments and information request - Clinical - information (numbered 1 through 7) regarding any changes to entries in the Biomedical Systems (BMS) IRC database & additional clinical PMC comment for 2017-02-09 telecon
February 9, 2017	Takeda/ARIAD discussion of possible new post-marketing commitment – T-con
February 10, 2017	Late cycle meeting for NDA 208772 scheduled for 2017-02-24 - Late-Cycle Meeting Background Package
February 10, 2017	PMC proposal for intracranial response rate of brigatinib and data extraction dates for Study AP26113-13-201
February 14, 2017	Response to FDA labeling review comments dated 2017-01-27 (SN# 0036)
February 16, 2017	Clinical inquiry from FDA - clarify whether radiographic images performed between February 29, 2016 and May 31, 2016 contributed to the IRC-assessed analyses of systemic and intracranial responses
February 17, 2017	Response to clinical review comments and information request dated 2017-02-16 (SN# 0037)
February 17, 2017	Response to FDA request 4057449 dated 2017-02-16 - Clinical - email response
February 21, 2017	Late cycle meeting for NDA 208772 scheduled for 2017-02-24 - ARIAD attendee list
February 22, 2017	FDA Request for Information - drug substance, starting material and intermediate impurity information
February 24, 2017	Type C Meeting (written response by 2017-03-29) on AP26113-16-202 - Briefing Package (SN# 0275)
February 24, 2017	ARIAD/FDA/Takeda late-cycle meeting to discuss review process and potential substantive findings
March 1, 2017	Response to clinical review comments and information request dated 2017-01-07 (SN# 0038)
March 1, 2017	FDA NDA review Information Request - Clinical - patients enrolled in AP26113-13-201 who had a medical history of diabetes or pre-diabetes at baseline
March 3, 2017	PLAIR request submitted to NDA 208772 for brigatinib 30 mg tablets - pre-approval importation request
March 7, 2017	PMC proposal to characterize duration of intracranial objective response - Follow-up to late-cycle meeting held 2017-02-24
March 7, 2017	Response to clinical review comments and RFI dated 2017-03-01 - patients enrolled in AP26113-13-201 who had a medical history of diabetes or pre-diabetes at baseline. A copy of this response was sent by email to FDA on 2017-03-03. (SN# 0039)
March 8, 2017	FDA NDA review comments and information request - Clinical - list of people who initiated/authorized the IRC database changes for Study AP26113-13-201
March 9, 2017	Source documentation for IRC database changes - ARIAD proposal in response to FDA teleconference request dated 2017-03-08
March 9, 2017	Response to clinical review comments and RFI dated 2017-03-08 - list of people who initiated/authorized the IRC database changes for Study AP26113-13-201. (SN# 0040)
March 10, 2017	Teleconference with FDA to discuss IRC database changes and clinical PMC for intracranial response
March 13, 2017	FDA Proposed Post Marketing Commitment - Clinical - Intracranial response duration
March 13, 2017	PLAIR request dated 2017-03-03 granted - CDER will allow the importation of NDA 208772 brigatinib 30 mg tablets under PLAIR

Contact Date	Title
March 13, 2017	Follow Up to 2017-03-10 RFI Response - Source Documentation for IRC Database Changes. A copy of this response was sent to FDA by email on 2017-03-13. (SN# 0041)
March 15, 2017	Late-Cycle Meeting Minutes - Official minutes of the meeting held 2017-02-24
March 15, 2017	Response to FDA's proposed Clinical PMC dated 2017-03-13 - Agreement on PMC for Intracranial response duration (SN# 0042)
March 20, 2017	FDA NDA review Information Request - Carton and Container Labeling - minor edits to storage temperature language
March 21, 2017	FDA rationale for 2017-03-20 Carton and Container Labeling Request for Information - to align with the definition and syntax of USP-defined controlled room temperature
March 22, 2017	Response to FDA request 4072064 dated 2017-03-20 - Bottle and Carton Labelling - Request FDA agreement with proposed response
March 27, 2017	FDA revised PMR - Clinical - require a confirmation of clinical benefit as opposed to establishing superiority over existing therapies
March 27, 2017	FDA NDA review comments and information request - Clinical - perform an analysis correlating creatine phosphokinase (CPK) elevation with any preferred term event of myalgia or muscle spasm
March 28, 2017	Response to 2017-02-22 FDA Request for Information - CMC Information Amendment - regarding the control of impurities in brigatinib drug substance, starting materials and intermediates and also introduces Ajinomoto OmniChem (OmniChem) as an additional drug substance manufacturer. (SN# 0281)
March 28, 2017	Response to proposed PMR Clinical dated 2017-03-27 - ARIAD agreement with FDA Revised Clinical PMR proposal dated 2017-03-27 (SN# 0043)
March 29, 2017	Type C Meeting Request - Written Responses - AP26113-16-202 - FDA written responses
March 29, 2017	Response to FDA Carton and Container (CMC) Labeling Review comments dated 2017-03-20 - minor edits to storage temperature language. (SN# 0044)
March 30, 2017	Response to clinical review comments and RFI dated 2017-03-27 - perform an analysis correlating creatine phosphokinase (CPK) elevation with any preferred term event of myalgia or muscle spasm. (SN# 0045)
April 3, 2017	Brigatinib label - FDA labeling comment dated 2017-04-03
April 11, 2017	Response to FDA labeling review comments dated 2017-04-03. A copy of this response was sent by email to FDA on 2017-04-10. (SN# 0046)
April 17, 2017	FDA NDA review comments and information request - Clinical - provide line listing of individual IRC-assessed intracranial efficacy response data from Study 201
April 18, 2017	Response to clinical review comments and information request dated 2017-04-17. A copy of this response was sent by email to FDA on 2017-04-18. (SN# 047)
April 19, 2017	Teleconference with FDA on 2017-04-19 - discussion of USPI Section 5.1 ILD and other serious pulmonary adverse reactions
April 24, 2017	Brigatinib label - FDA labeling comment dated 2017-04-24
April 25, 2017	Response to FDA labeling review comments dated 2017-04-24 (SN# 0048)
April 26, 2017	Brigatinib label - FDA labeling comment dated 2017-04-26
April 26, 2017	Teleconference with FDA on 2017-04-26 - Additional slides submitted to FDA for discussion - USPI clarification
April 26, 2017	Response to FDA labeling review comments dated 2017-04-26 (SN# 0049)
April 27, 2017	Brigatinib label - FDA labeling comment dated 2017-04-27
April 27, 2017	Response to FDA labeling review comments dated 2017-04-27 (SN# 0050)
April 28, 2017	Accelerated Approval Letter - NDA 208772 for Alunbrig - 30 mg and 90 mg tablets



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
12/736,910	01/17/2012	Yihan Wang	13396-020-999	42031

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 06/20/2017 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

✕ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Kunyong Yang/
Name:	Kunyong Yang
Registration Number:	64629

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Wang <i>et al.</i>	Confirmation No.:	5957
Patent No.:	9,012,462	Issued on:	April 21, 2015
Application No.:	12/736,910	Art Unit:	1626
Filing or 371(c):	January 17, 2012	Examiner:	Cheng, Karen
For:	PHOSPHORUS DERIVATIVES AS KINASE INHIBITORS	Attorney Docket No.:	13396-020-999 (previous 11932.0011-00000) CAM: 209362-999020

**REQUEST FOR RECONSIDERATION OF
DECISION OF REDETERMINATION OF PATENT TERM ADJUSTMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Patentee hereby requests reconsideration of the Office's decision of Redetermination of Patent Term Adjustment mailed February 22, 2017, and issuance of a revised determination of patent term adjustment along with a corresponding certificate of correction to correct the patent term adjustment in accordance with the remarks provided herein. Applicants request a two (2) month extension of time from April 22, 2017 to June 22, 2017 for filing a request for reconsideration. Accordingly, this request is timely filed.

The Office has re-determined the patent term adjustment (PTA) to be 626 days. For the reasons set forth below, Patentee respectfully submits that the correct PTA is **591 days**.

I. Relevant Procedural History and Statement of the Facts

U.S. Patent No. 9,012,462 ("the '462 patent") was granted by the U.S. Patent and Trademark Office ("the Office") on April 21, 2015, with a calculated PTA under 35 U.S.C. § 154(b) of 752 days. Patentee filed an Application for Patent Term Adjustment pursuant to 37 C.F.R. § 1.705(b) on June 22, 2015, requesting a redetermination of the PTA to 596 days. In response, the Office mailed a Decision of Redetermination of Patent Term Adjustment ("First PTA Decision") on February 24, 2016, re-determining the PTA to be 436 days.

Patentee then filed a Request for Reconsideration of Decision of Reconsideration of Patent Term Adjustment on September 22, 2016, requesting a redetermination of the PTA to 591 days. In response, the Office mailed a Decision of Redetermination of Patent Term Adjustment (“Second PTA Decision”) on February 22, 2017, re-determining the PTA to be 626 days.¹

II. Calculation of Patent Term Adjustment

With the exception of the Office’s calculation of applicant delay associated with the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012, and thus its calculation of the total PTA, Patentee agrees with the Office’s calculations set forth in the Decision. Specifically, Patentee agrees with the Office’s determinations that:

- the period of A delay is 439 days. Second PTA Decision, page 2.
- the period of B delay is 448 days. *Id.*
- the period of C delay is 0 days. *Id.*
- the period of Overlap is 0 days. *Id.*

Additionally, Patentee agrees with the Office’s determination of applicant delay as follows:

- 126 days of applicant delay related to the filing of the response to Notification of Missing Requirements (beginning on March 8, 2011 and ending on July 11, 2011). Second PTA Decision, page 2; *see also* First PTA Decision, page 5.
- 32 days of applicant delay related to the filing of the response to non-final Office Action (beginning on December 21, 2013 and ending on January 21, 2014). Second PTA Decision, page 2.
- 88 days of applicant delay related to the filing of Request for Continued Examination and response to final Office Action (beginning on June 24, 2014 and ending on September 19, 2014). Second PTA Decision, page 2; *see also* First PTA Decision, page 6.

¹ A Certificate of Correction was issued on June 6, 2017, stating that the PTA for the subject patent is 436 days. It appears that the Certificate of Correction was mistakenly issued by the Office based on the First PTA Decision. As of filing of this request, the current PTA, as shown under the Patent Term Adjustment tab in the Patent Applicant Information Retrieval (PAIR) system, remains as 626 days.

- 15 days of applicant delay related to the filing of 37 C.F.R. § 1.312 amendment after Notice of Allowance (beginning on February 23, 2015 and ending on March 9, 2015). Second PTA Decision, page 2.

The only remaining dispute between Patentee and the Office is the number of PTA days, if any, related to the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012.

The relevant portion of the prosecution history for this request is summarized as follows:

Patentee and the Office are now in agreement that the commencement date is Monday, **November 22, 2010**.

A Notification of Missing Requirements under 35 U.S.C. 371 was mailed by the Office on December 6, 2010. Patentee and the Office are now in agreement that the deadline for Applicant to file a response without incurring applicant delay was Monday, March 7, 2011. A response to the Notification and a Petition under 37 C.F.R. § 1.47(a) were mailed by Applicant on July 6, 2011 and received by the Office on **July 11, 2011**.

The Office mailed a Decision dismissing Applicant's Petition under 37 C.F.R. § 1.47(a) on **September 13, 2011** as lacking an item necessary to grant the petition. The Office set a two-month period (extendable under 37 C.F.R. § 1.136(a)) for Applicant to file a response to request reconsideration on the merits of the petition. Decision of September 13, 2011, page 2.

A Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) was filed by Applicant on **January 17, 2012**.

The Office mailed a Decision granting Applicant's Petition under 37 C.F.R. § 1.47(a) on April 12, 2012.

In the Request for Reconsideration of Decision of Reconsideration of Patent Term Adjustment filed September 22, 2016, Patentee submitted that there are 35 days of applicant delay related to the filing of the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a) on January 17, 2012.

In response, the Office considers that the 35 days of applicant delay suggested by the Patentee “is not warranted”. Second PTA Decision, page 2. No further explanation is provided by the Office. Patentee respectfully disagrees and reiterates that there are 35 days of applicant delay under 37 C.F.R. § 1.704(b), which provides:

With respect to the grounds for adjustment set forth in §§ 1.702(a) through (e), and in particular the ground of adjustment set forth in § 1.702(b), an applicant shall be deemed to have failed to engage in reasonable efforts to conclude processing or examination of an application for the cumulative total of any periods of time in excess of three months that are taken to reply to any notice or action by the Office making any rejection, objection, argument, or other request, measuring such three-month period from the date the notice or action was mailed or given to the applicant, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date that is three months after the date of mailing or transmission of the Office communication notifying the applicant of the rejection, objection, argument, or other request and ending on the date the reply was filed. The period, or shortened statutory period, for reply that is set in the Office action or notice has no effect on the three-month period set forth in this paragraph.

37 C.F.R. § 1.704(b) (emphasis added). *See also*, MPEP § 2732 (“The three-month period in 37 CFR 1.704(b) applies to the Office notices and letters issued as part of the pre-examination processing of an application.”).

In the Decision of September 13, 2011, after reviewing Applicant’s Petition under 37 C.F.R. § 1.47(a) and its supporting documents, the Office dismissed the petition based on the reasoning that “[i]t is not clear that the inventors have been presented with a complete copy of the application papers, including the declaration” and that “[f]urther, it does not appear that Mr. Bernstein has firsthand knowledge of points six and seven from the statement of facts.” Decision of September 13, 2011, pages 1–2. Patentee respectfully submits that the Decision of September 13, 2011 is a “rejection” or “objection” to Applicant’s Petition under 37 C.F.R. § 1.47(a) and the Office’s reasoning is an “argument” within the meaning of 37 C.F.R. § 1.704(b).

Moreover, the Office set a two-month period (extendable under 37 C.F.R. § 1.136(a)) for Applicant to file a response. Decision of September 13, 2011, page 2. Patentee respectfully submits that the Decision of September 13, 2011 is also a “request” within the meaning of 37 C.F.R. § 1.704(b).

Accordingly, Patentee respectfully submits that C.F.R. § 1.704(b) is applicable to a response to the Decision of September 13, 2011.

The three-month date to respond to the Decision of September 13, 2011 was **December 13, 2011**. A response—the Request for Reconsideration of Petition under 37 C.F.R. § 1.47(a)—was filed on **January 17, 2012**. Accordingly, Patentee respectfully submits that there are 35 days of applicant delay under 37 C.F.R. § 1.704(b) beginning on December 14, 2011 and ending on January 17, 2012.

III. Overall Patent Term Adjustment Calculation

The overall applicant delay:

$$126 + 35 + 32 + 88 + 15 = 296$$

The overall PTA:

$$\begin{aligned} & \text{A delay} + \text{B delay} + \text{C delay} - \text{Overlap} - \text{applicant delay} \\ &= 439 + 448 + 0 - 0 - 296 \\ &= 591 \end{aligned}$$

Therefore, Patentee respectfully submits that the correct patent term adjustment under 35 U.S.C. § 154(b) is **591 days**.

IV. Conclusion

Reconsideration of the Decision and correction of the Patent Term Adjustment calculation are respectfully requested.

An extension of time fee of \$600 for a period of two months is believed to be due for the submission of this paper. The fees will be paid via EFS Web. If any other fees are deemed necessary for the submission of this paper, the Director is authorized to charge the required fees to Jones Day Deposit Account No. 50-3013 (Ref.: 209362-999020).

Respectfully submitted,

Date: June 20, 2017

/Kunyong Yang/

Kunyong Yang

Reg. No. 64,629

For: Dale Rieger

Reg. No. 43,045

JONES DAY

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Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

SEP 27 2017

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 9,012,462 was filed on June 21, 2017, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application ALUNBRIG® (brigatinib), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).



Mary C. Till

Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Dale L. Rieger, Ph.D.
Jones Day
250 Vesey Street
New York, NY 10281-1047