IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of	:	Attorney Docket No. 2015-1680
Frank R. Busch et al.	:	
Patent No. 6,673,929	:	
Issued January 6, 2004	:	
PROCESS FOR PREPARING GROWTH HORMONE SECRETAGOGUES	:	Mail Stop: Hatch-Waxman PTE

APPLICATION FOR PATENT TERM EXTENSION
UNDER 35 U.S.C. § 156

Mail Stop Hatch-Waxman PTE
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant, RaQualia Pharma Inc., (a corporation of Japan and having a place of business at 1-21-19 Meieki Minami, Nakamura-ku, Nagoya-shi, Aichi, 450-0003, Japan) hereby applies for an extension of the term for U.S. Patent No. 6,673,929 under 35 U.S.C. §156. In accordance with 37 C.F.R. §1.740, RaQualia Pharma Inc. states the following in support of this application:

1. Description of Applicant required by 35 U.S.C. §156(d)(1) and MPEP §2752.

RaQualia Pharma Inc. is the owner of the entire right, title, and interest in U.S. Patent No. 6,673,929 by virtue of an assignment from, the previous assignee, Pfizer Inc., to RaQualia Pharma Inc. (recorded at the U.S. Patent and Trademark Office on January 22, 2010 at Reel 023832, Frame 0575; change of address of RaQualia Pharma Inc. was recorded on July 12, 2016). Pfizer Inc. was the previous owner of the entire right, title, and interest in U.S. Patent No. 6,673,929 by virtue of an assignment from the named inventors, Frank R. Busch, Charles K. Chiu, Clifford N. Meltz, Ronald J. Post, and Peter

R. Rose, to Pfizer Inc. (recorded at the U.S. Patent and Trademark Office on October 30, 2002 at Reel 013476, Frame 0190). See **Exhibit 19.**

2. Information required by 37 C.F.R. §1.740(a)(1).

The approved product is ENTYCE® (capromorelin oral solution). The U.S. Food and Drug Administration ("FDA") has approved NADA No. 141-457 for use of ENTYCE® (capromorelin oral solution) for appetite stimulation in dogs.

The approved product ENTYCE® is further identified as follows:

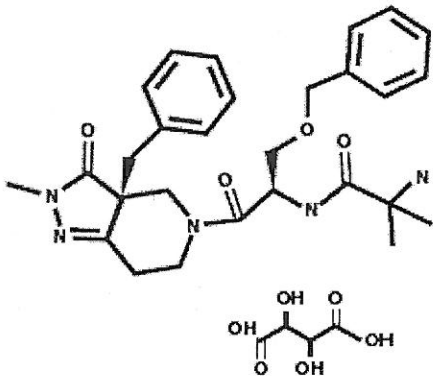
Chemical Name: 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartrate

Generic Name: capromorelin tartrate

Molecular Formula: $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_6$

Molecular Weight: 655.70 Daltons

Chemical Formula:



The active ingredient in ENTYCE® is the compound capromorelin.
ENTYCE® (capromorelin oral solution) is a selective ghrelin receptor agonist that binds to receptors and affects signaling in the hypothalamus to cause appetite stimulation and

binds to the growth hormone secretagogue receptor in the pituitary gland to increase growth hormone secretion.

ENTYCE® is supplied as a 30 mg/mL flavored solution in 10 mL, 15 mL, and 30 mL bottles with a measuring syringe.

More information regarding the approved product may be found in the following Exhibits enclosed herewith.

A copy of the FDA's approval letter is enclosed as **Exhibit 1.**

A copy of the Freedom of Information Summary is enclosed as **Exhibit 2.**

A copy of the approved U.S. product label and package insert for ENTYCE® is enclosed as **Exhibit 3**.

3. Relationship of Applicant to the Marketing Applicant required by MPEP §2752.

The Marketing Applicant identified in NADA No. 141-457 is Aratana Therapeutics, Inc., a corporation duly organized and existing under the laws of the State of Delaware, United States of America.

Aratana Therapeutics, Inc. is the licensee of U.S. Patent No. 6,673,929 from the patent owner RaQualia Pharma Inc. The license remains in effect.

There is an agency relationship between the patent owner(s) and the Marketing Applicant during the regulatory review period.

As suggested in MPEP § 2752, there is enclosed as **Exhibit 4** a letter from the Marketing Applicant to the patent owner, showing that the patent owner is authorized to rely upon the activities of the Marketing Applicant before the FDA in submission of this Application for Patent Term Extension under 35 U.S.C. § 156.

4. Information required by 37 C.F.R. §1.740(a)(2).

The FDA's regulatory review of ENTYCE® was conducted under Section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360b).

5. Information required by 37 C.F.R. §1.740(a)(3).

The FDA approved ENTYCE® for commercial marketing or use under 21 U.S.C. §360b on May 16, 2016. See **Exhibit 1**, page 3.

6. Information required by 37 C.F.R. §1.740(a)(4).

The active ingredient in ENTYCE ® is the compound capromorelin. Capromorelin 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.

7. Information required by 37 C.F.R. §1.740(a)(5).

This application for patent term extension is being submitted within 60 days of the date of FDA approval of ENTYCE ® for commercial marketing or use under 21 U.S.C. §360b. The date of FDA approval is May 16, 2016. See **Exhibit 1**. The last date this application can be submitted is July 14, 2016.

8. Information required by 37 C.F.R. §1.740(a)(6).

The patent for which Applicant requests an extension is U.S. Patent 6,673,929. This patent is identified as follows:

Inventors:
Frank R. Busch
Charles K. Chiu
Clifford N. Meltz

Ronald J. Post
Peter R. Rose

Patent No: 6,673,929

Title: Process for Preparing Growth Hormone Secretagogues

First priority date: February 26, 1999 (U.S. Provisional Application No. 60/122,745)
U.S. Filing Date for Calculating Patent Term: February 1, 2000 (U.S. Patent No. 6,673,929 issued from U.S. Application No. 10/283,720, filed October 30, 2002, which is a division of U.S. Application No. 09/496,075, filed February 1, 2000, now U.S. Patent No. 6,541,634)

Date of Issue: January 6, 2004

Patent Term Adjustment (PTA): 12 days

Date of expiration: February 13, 2020

9. Document required by 37 C.F.R. §1.740(a)(7).

A copy of the entire specification for U.S. Patent 6,673,929, including the claims and drawings, is enclosed as **Exhibit 5**.

10. Information and documents required by 37 C.F.R. §1.740(a)(8).

No disclaimer or reexamination certificate has issued for U.S. Patent No. 6,673,929. All maintenance fees have been paid. A statement evidencing the maintenance fee payments for the patent is enclosed as **Exhibit 6**.

11. Information required by 37 C.F.R. §1.740(a)(9).

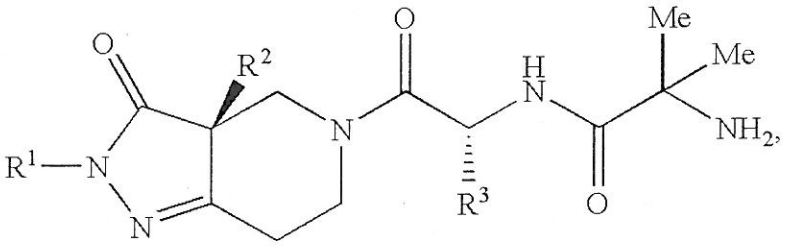
U.S. Patent No. 6,673,929 claims the approved product, ENTYCE®. More specifically, claims 19-26, 28-32, 34-39, and 41-45 encompass methods of making capromorelin, the active ingredient in ENTYCE®. The manner in which the claims read on ENTYCE® is more specifically described as follows:

Claim 19:

Claim 19 recites the following:

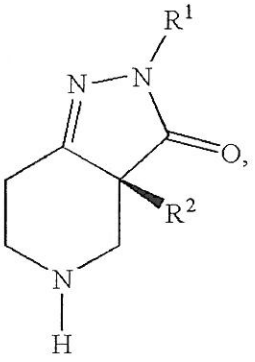
19. A process for preparing a compound of Formula III,

III



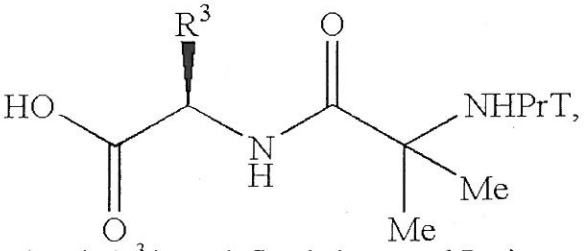
wherein:
R^1 is —(C_1-C_{10})alkyl optionally substituted with up to three fluoro atoms;
R^2 is phenylmethyl or 2-pyridylmethyl; and
R^3 is —(C_1-C_5)alkyl-O—(C_0-C_5)alkylphenyl, where the phenyl substituent in the definition of R^3 is optionally substituted with up to three fluoro atoms,
comprising:
a) mixing an appropriate chiral tartrate salt having the structure of Formula IV,

IV



D- or L-tartaric acid
wherein R^1 and R^2 are as defined above,
and an organic amine in a reaction inert solvent at a temperature of about −68° C. to about −45° C. to form a slurry;
b) adding a compound of the Formula V,

V



wherein R^3 is as defined above and Prt is an amine protecting group, to said slurry to form a reaction mixture comprising the tartrate salt of the organic amine, the free base of a compound of Formula IV and a compound of the Formula V;

c) adding a coupling reagent to said reaction mixture to form a compound of Formula II; and
d) reacting said compound of Formula II with a suitable deprotecting reagent to form a compound of Formula III.

Claim 19 covers a method of making the compound capromorelin. Therefore, claim 19 reads on the approved product ENTYCE®. Please note that Formula II recited in claim 19 can be found in Claim 1 of the patent. See **Exhibit 5**.

Claim 20:

Claim 20 recites the following:

20. A process of claim 19 wherein said compound of Formula IV is suspended in said solvent prior to the addition of said organic amine comprising the additional step of warming said slurry to about −50° C. to about −40° C. prior to step b.

Claim 20 covers a method of making the compound capromorelin. Therefore, claim 20 reads on the approved product ENTYCE®.

Claim 21:

Claim 21 recites the following:

21. A process of claim 20 wherein said Prt is tert-butyloxycarbonyl and said tert-butyloxycarbonyl is removed by reacting said compound of Formula II with an acid.

Claim 21 covers a method of making the compound capromorelin. Therefore, claim 21 reads on the approved product ENTYCE®. Please note that Formula II recited in claim 21 can be found in Claim 1 of the patent. See **Exhibit 5**.

Claim 22:

Claim 22 recites the following:

22. A process of claim 21 wherein said acid is methanesulfonic acid.

Claim 22 covers a method of making the compound capromorelin. Therefore, claim 22 reads on the approved product ENTYCE®.

Claim 23:

Claim 23 recites the following:

23. A process of claim 22 wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

Claim 23 covers a method of making the compound capromorelin. Therefore, claim 23 reads on the approved product ENTYCE®.

Claim 24:

Claim 24 recites the following:

24. A process of claim 23 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

Claim 24 covers a method of making the compound capromorelin. Therefore, claim 24 reads on the approved product ENTYCE®.

Claim 25:

Claim 25 recites the following:

25. A process of claim 24 wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

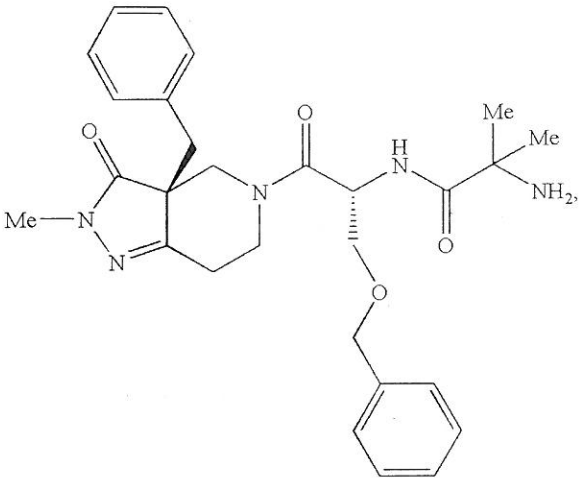
Claim 25 covers a method of making the compound capromorelin. Therefore, claim 25 reads on the approved product ENTYCE®.

Claim 26:

Claim 26 recites the following:

26. A process of claim 24 wherein a compound of formula IIIA,

IIIA



is prepared.

Claim 26 covers a method of making the compound capromorelin. Therefore, claim 26 reads on the approved product ENTYCE®.

Claim 28:

Claim 28 recites the following:

28. A process of claim 21 wherein said acid is trifluoroacetic acid.

Claim 28 covers a method of making the compound capromorelin. Therefore, claim 28 reads on the approved product ENTYCE®.

Claim 29:

Claim 29 recites the following:

29. A process of claim 28 wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

Claim 29 covers a method of making the compound capromorelin. Therefore, claim 29 reads on the approved product ENTYCE®.

Claim 30:

Claim 30 recites the following:

30. A process of claim 29 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

Claim 30 covers a method of making the compound capromorelin. Therefore, claim 30 reads on the approved product ENTYCE®.

Claim 31:

Claim 31 recites the following:

31. A process of claim 30 wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

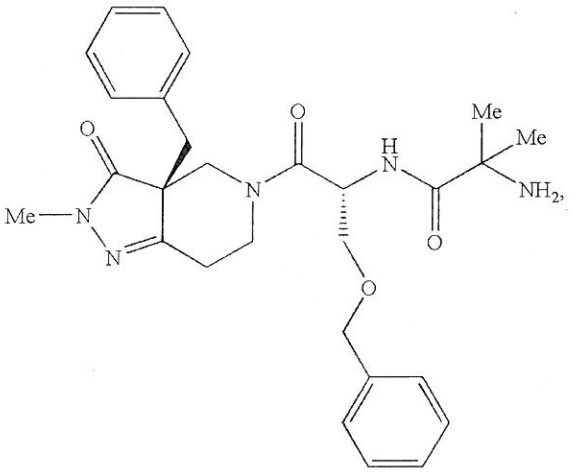
Claim 31 covers a method of making the compound capromorelin. Therefore, claim 31 reads on the approved product ENTYCE®.

Claim 32:

Claim 32 recites the following:

32. A process of claim 30 wherein a compound of formula IIIA,

IIIA



is prepared.

Claim 32 covers a method of making the compound capromorelin. Therefore, claim 32 reads on the approved product ENTYCE®.

Claim 34:

Claim 34 recites the following:

34. A process of claim 19 wherein said Prt is tert-butyloxycarbonyl and said tert-butyloxycarbonyl is removed by reacting said compound of Formula II with an acid.

Claim 34 covers a method of making the compound capromorelin. Therefore, claim 34 reads on the approved product ENTYCE®. Please note that Formula II recited in claim 34 can be found in Claim 1 of the patent. See **Exhibit 5**.

Claim 35:

Claim 35 recites the following:

35. A process of claim 34 wherein said acid is methanesulfonic acid.

Claim 35 covers a method of making the compound capromorelin. Therefore, claim 35 reads on the approved product ENTYCE®.

Claim 36:

Claim 36 recites the following:

36. A process of claim 35 wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step f, said coupling reagent is propane phosphonic acid anhydride.

Claim 36 covers a method of making the compound capromorelin. Therefore, claim 36 reads on the approved product ENTYCE®.

Claim 37:

Claim 37 recites the following:

37. A process of claim 36 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

Claim 37 covers a method of making the compound capromorelin. Therefore, claim 37 reads on the approved product ENTYCE®.

Claim 38:

Claim 38 recites the following:

38. A process of claim 37 wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide.

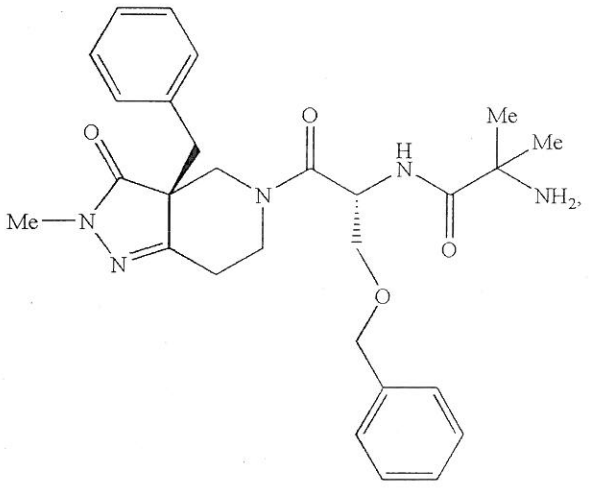
Claim 38 covers a method of making the compound capromorelin. Therefore, claim 38 reads on the approved product ENTYCE®.

Claim 39:

Claim 39 recites the following:

39. A process of claim 37 wherein a compound of formula IIIA,

IIIA



is prepared.

Claim 39 covers a method of making the compound capromorelin. Therefore, claim 39 reads on the approved product ENTYCE®.

Claim 41:

Claim 41 recites the following:

41. A process of claim 34 wherein said acid is trifluoroacetic acid.

Claim 41 covers a method of making the compound capromorelin. Therefore, claim 41 reads on the approved product ENTYCE®.

Claim 42:

Claim 42 recites the following:

42. A process of claim 41 wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step f, said coupling reagent is propane phosphonic acid anhydride.

Claim 42 covers a method of making the compound capromorelin. Therefore, claim 42 reads on the approved product ENTYCE®.

Claim 43:

Claim 43 recites the following:

43. A process of claim 42 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

Claim 43 covers a method of making the compound capromorelin. Therefore, claim 43 reads on the approved product ENTYCE®.

Claim 44:

Claim 44 recites the following:

44. A process of claim 43 wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide.

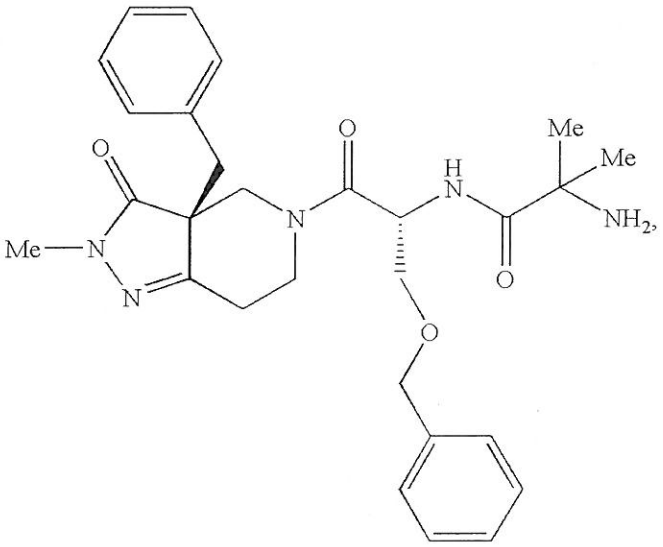
Claim 44 covers a method of making the compound capromorelin. Therefore, claim 44 reads on the approved product ENTYCE®.

Claim 45:

Claim 45 recites the following:

45. A process of claim 43 wherein a compound of formula IIIA,

IIIA



is prepared.

Claim 45 covers a method of making the compound capromorelin. Therefore, claim 45 reads on the approved product ENTYCE®.

12. Information required by 37 C.F.R. §1.740(a)(10).

The relevant dates and information pursuant to 35 U.S.C. §156(g) as defined by 37 C.F.R. §1.740(10)(ii) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Beginning of Testing Phase

(a) Appetite Stimulation Study (Study No. 7B61W-60-02-371) commenced on December 5, 2002 by Pfizer Inc. to evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs. See **Exhibit 7**.

(b) The Appetite Stimulation Study Number 7B61W-60-02-371 described in item (a) above is completed on December 23, 2002. See **Exhibit 7**.

(c) Appetite Stimulation Study (Study No. 7B61W-60-03-380) commenced on January 23, 2003 by Pfizer Inc. to evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs. See **Exhibit 8**.

(d) Appetite Stimulation Study (Study No. 7B61W-60-03-381) commenced on January 23, 2003 by Pfizer Inc. to evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed and neutered beagle dogs following ten daily oral doses of 1 mg/kg. See **Exhibit 9**.

(e) The Appetite Stimulation Study Number 7B61W-60-03-380 described in item (c) above is completed on February 11, 2003. See **Exhibit 8**.

(f) The Appetite Stimulation Study Number 7B61W-60-03-381 described in item (d) above is completed on February 11, 2003. See **Exhibit 9**.

(g) U.S. Patent No. 6,673,929 issued on January 6, 2004.

(h) As shown in the Chronology Table below, between January 6, 2004, and January 22, 2010, numerous activities took place to develop capromorelin including: additional studies involving capromorelin; business decisions made by Pfizer, including Pfizer's decision to close the Pfizer Global Research & Development Nagoya where capromorelin was being developed; the transfer of assets from Pfizer to RaQualia; and RaQualia's search for a development partner culminating in an agreement with Aratana. Please see the entries in the chronology table for further details showing that the development of capromorelin was ongoing during this period.

(i) Pfizer Inc. assigns U.S. Patent No. 6,673,929 to RaQualia Pharma Inc. on January 22, 2010.

(j) Investigational New Animal Drug (INAD) Application, covering ENTYCE® (capromorelin oral solution) in dog species, was filed by Aratana Therapeutics, Inc. with the FDA on November 1, 2011, pursuant to Subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act. The FDA granted and assigned INAD Application No. 012-103 in a letter dated November 2, 2011. See **Exhibit 10**.

(k) Proof of Concept Clinical Field Study to Evaluate the Effectiveness of AT-002 on Appetite in Dogs (Study No. AT002-CCL-12-001) commenced on August 6, 2012, by Aratana Therapeutics, Inc. See **Exhibit 11.**

(l) AT-002 Dose Titration Study in Adult Beagle Dogs (Study No. AT-002-CCL-13-002) commenced on April 29, 2013 by Xenometrics, LLC for Aratana Therapeutics, Inc. See **Exhibit 12.**

(m) AT-002 Dose Titration Study Number AT-002-CCL-13-002 described in item (l) above is completed on August 1, 2013. See **Exhibit 13.**

(n) Pivotal Clinical Field Study to Evaluate the Safety and Effectiveness of AT-002 on Stimulation of Appetite in Dogs (Study No. AT002-CCL-13-003) commenced on January 2, 2014 by Aratana Therapeutics, Inc. See **Exhibit 14.**

(o) AT-002: Pharmacokinetic Comparison of Two Formulations in a Cross-Over Design in Beagle Dogs for Two Dose Levels (Study No. 031599; Aratana Ref. No. AT002-CPK-14-007) commenced on January 3, 2014 by Ricerca Biosciences, LLC. for Aratana Therapeutics, Inc. See **Exhibit 15**.

(p) Proof of Concept Clinical Field Study Number AT002-CCL-12-001 described in (k) above is completed on February 20, 2014, by Aratana Therapeutics, Inc. See **Exhibit 11.**

(q) AT-002: Four Day Repeat Dose Food Consumption Study in Beagle Dogs (Study No. 031805; Aratana Ref. No. AT002-CCL-14-004) is completed on August 6, 2014 by Ricerca Biosciences, LLC for Aratana Therapeutics, Inc. See **Exhibit 16.**

(r) Pharmacokinetic Comparison Study Number 031599 (Aratana Ref. No. AT002-CPK-14-007) described in item (o) above is completed on August 14, 2014. See **Exhibit 17.**

(s) Pivotal Clinical Field Study Number AT002-CCL-13-003 described in item (n) above is completed on August 25, 2015. See **Exhibit 14.**

End of Testing Phase and Beginning of Approval Phase

The NADA (NADA No. 141-457) was filed on March 21, 2016. See **Exhibit 18**.

End of Approval Phase

NADA No. 141-457 was approved on May 16, 2016. See **Exhibit 1**.

13. Information required by 37 C.F.R. §1.740(a)(11).

The following is a brief description of significant activities undertaken by or for Applicant during the applicable regulatory period with respect to ENTYCE® (including significant dates applicable to such activities):

CHRONOLOGY TABLE, INCLUDING KEY REGULATORY CORRESPONDENCE BETWEEN ARATANA THERAPEUTICS INC. AND CENTER FOR VETERINARY MEDICINE (CVM)/FDA

Date	Source	Description of correspondence
10/9/2002	Midwest Research Institute/Pfizer	Pfizer begins Safety of CP-424, 391-18 in Cats Study No. 7481R-60-02-250 by Midwest Research Institute for Pfizer Inc. for studying the safety of capromorelin in cats. See **Exhibit 20**.
11/13/2002	Pfizer	Pfizer begins Companion Animal Appetite Stimulation Study No. 7B81W-60-02-256 to determine the orexigenic effects of CP-477,355-18 or CP-424,391-18 when administered concurrently with chemotherapy in normal adult male and female cats. See **Exhibit 21.**
12/2/2002	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B81W-60-02-264 to evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed/neutered cats following ten daily oral capsule doses of 0.33, 1, 3, 10 or 15 mg/kg. See **Exhibit 22.**
12/3/2002	Pfizer	Pfizer completes the Companion Animal Appetite Stimulation Study Number 7B81W-60-02-256. See **Exhibit 21**.

12/5/2002	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B61W-60-02-371 to evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs. See **Exhibit 7**.
12/20/2002	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B81W-60-02-264. See **Exhibit 22.**
12/23/2002	Pfizer	Pfizer completes the Appetite Stimulation Study Number 7B61W-60-02-371. See **Exhibit 7**.
1/23/2003	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B61W-60-03-380 to evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs. See **Exhibit 8**.
1/23/2003	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B61W-60-03-381 to evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed and neutered beagle dogs following ten daily oral doses of 1 mg/kg. See **Exhibit 9.**
1/28/2003	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B81W-60-03-269 to evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed/neutered cats following ten daily oral tablet doses of 5, 10 or 20 mg. See **Exhibit 23**.
2/11/2003	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B61W-60-03-380 on February 11, 2003. See **Exhibit 8**.
2/11/2003	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B61W-60-03-381 on February 11, 2003. See **Exhibit 9**.
2/16/2003	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B81W-60-03-269 on February 16, 2003. See **Exhibit 23**.

3/3/2003	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B81W-60-03-272 to evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed/neutered cats following eight daily oral tablet doses 3 mg. See **Exhibit 24**.
3/7/2003	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B81W-60-03-273 to evaluate the effects of CP-424,391-18 as an appetite stimulant in intact cats when administered as a tablet at ~0.5, 1 or 2 mg/kg. See **Exhibit 25**.
3/20/2003	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B81W-60-03-272 on March 20, 2003. See **Exhibit 24.**
3/23/2003	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B81W-60-03-273 on March 23, 2003. See **Exhibit 25**.
9/11/2003	Pfizer	Pfizer begins Appetite Stimulation Study No. 7B81W-60-02-246 to evaluate the effects of CP-424,391-18 and CP-477,335-18 as appetite stimulants in spayed/neutered cats following ten daily oral capsule doses 3 and 1 mg/kg, respectively. See **Exhibit 26**.
9/24/2003	Pfizer	Pfizer begins Field Efficacy and Safety of CP-424,391 in Inappetent Cats (Study No. 1982R-60-03-302). See **Exhibit 27.**
9/30/2003	Pfizer	Pfizer completes Appetite Stimulation Study Number 7B81W-60-02-246 on September 30, 2003. See **Exhibit 26**.
11/7/2003	Pfizer	Pfizer completes Safety of CP-424,391-18 Study Number 7481R-60-02-250 on November 7, 2003. See **Exhibit 20.**
1/6/2004	USPTO	U.S. Patent No. 6,673,929 is issued.

12/4/2004	Pfizer	Pfizer begins Field Efficacy and Safety of CP-424,391 in Inappetent Cats in the EU (Study No. 5982R-10-03-234). See **Exhibit 28.**
6/21/2005	Pfizer	Pfizer completes Field Efficacy and Safety of CP-424,391 Study number 5982R-10-03-234 on June 21, 2005. See **Exhibit 28.**
3/27/2006	Pfizer	Pfizer completes Field Efficacy and Safety of CP-424,391 Study number 1982R-60-03-302 on March 27, 2006, which began on September 24, 2003. See **Exhibit 27.**
12/1/2007	Pfizer/RaQualia	Pfizer evaluates forming start-up/spinoff company that would become RaQualia. See **Exhibit 29**.
3/10/2008	Pfizer/RaQualia	An inventory list of all dosages and formulations of capromorelin (CP-424,391) is completed. See **Exhibit 30**.
3/11/2008	Pfizer/RaQualia	Ongoing characterization of capromorelin continued as evidenced by communications between Pfizer Japan and Pfizer Inc. See **Exhibit 31**.
6/30/2008	Pfizer/RaQualia	Intellectual Property Transfer & License Agreement (IPTA) is executed between Pfizer Inc. and RaQualia Pharma Inc. See **Exhibit 32**.
11/12/2008	Pfizer/RaQualia	Pfizer requests confirmation from RaQualia of its desire to continue patent prosecution of the families of the patent applications associated with capromorelin evidenced by an email from Pfizer Inc. to RaQualia. See **Exhibit 33**.
11/19/2008	Pfizer/RaQualia	RaQualia expresses desire to maintain patent protection for capromorelin as evidenced by a communication between RaQualia and Pfizer Inc. See **Exhibit 34**.

12/12/2008	Pfizer/RaQualia	RaQualia expresses desire to have patent applications for capromorelin assigned to RaQualia as evidenced by a communication between RaQualia and Pfizer Inc. See **Exhibit 35**.
5/26/2009	Pfizer	Pfizer begins Study Protocol Human Lymphocyte Assay of CP-424391M22 (Study Number: 09GR125). See **Exhibit 36**.
7/13/2009	Pfizer/RaQualia	An inventory list of all dosages and formulations of capromorelin (CP-424,391) is updated. See **Exhibit 37**.
10/14/2009	Pfizer	Pfizer begins Exploratory Bioluminescence Ames Assay of M22 Metabolite of CP-424,391 (Study Number: 2009-3QB-GN). See **Exhibit 38**.
10/19/2009	Pfizer	Pfizer begins Exploratory In Vitro Micronucleus Assay of the M22 Metabolite of CP-424,391 (Study Number: CP-424391-2009-3QM-GN). See **Exhibit 39**.
11/19/2009	Pfizer	Pfizer continues to extract reports and files associated with capromorelin from Pfizer archives to transfer to RaQualia to continue development of the product as evidenced by emails between RaQualia and Pfizer. See **Exhibit 40**.
12/11/2009	RaQualia	RaQualia completes Program Transfer Report for the transfer of the ghrelin agonist (capromorelin) from Pfizer to RaQualia. See **Exhibit 41**.
12/15/2009	Pfizer/RaQualia	RaQualia and Pfizer complete Asset Transfer from Pfizer to RaQualia. See **Exhibit 42**.
1/22/2010	Pfizer/RaQualia	Pfizer assigned U.S. Patent No. 6,673,929 to RaQualia Pharma Inc.
5/24/2010	RaQualia/Aratana	RaQualia continues discussions with Aratana to form a partnership to develop capromorelin in domestic animals as evidenced by emails between RaQualia and Aratana. See **Exhibit 43**.

6/28/2010	RaQualia/ Animal Health Company	RaQualia enters into a Confidential Disclosure Agreement with Animal Health Company regarding RQ-00000005 for veterinary indications.
6/29/2010	RaQualia/ MPM Asset Management	RaQualia enters into a Confidential Disclosure Agreement with MPM Asset Management, LLC regarding the evaluation and negotiation of potential transactions between the parties for RaQualia programs.
7/6/2010	RaQualia/ Animal Health Company	RaQualia enters into a Confidential Disclosure Agreement with Animal Health Company regarding RQ-00000005 for veterinary indications.
12/27/2010	RaQualia/Aratana	RaQualia an Aratana executed an exclusive license agreement for RQ-00000005 for veterinary indications
2/24/2011	Aratana	Aratana held a Board of Directors meeting on February 24, 2011, where a Clinical Update was provided regarding AT-002 (capromorelin). See **Exhibit 44.**
4/29/2011	Aratana	Aratana held a Board of Directors meeting on April 29, 2011, where a Clinical Update was provided regarding AT-002 (capromorelin). See **Exhibit 44**.
6/28/2011	Aratana and CVM/FDA	Aratana held informational meeting with IVET (Innovation Exploration Team) of CVM/FDA.
6/29/2011	Aratana	Aratana held a Board of Directors meeting on June 29, 2011, where a Clinical Update was provided regarding AT-002 (capromorelin). See **Exhibit 44.**
10/12/2011	Aratana	Aratana held a Board of Directors meeting on October 12, 2011, where a Clinical Update was provided regarding AT-002 (capromorelin). See **Exhibit 44.**
11/1/2011	Aratana	Aratana requested establishment of an Investigational New Animal Drug (INAD) File for investigational evaluation of ENTYCE® for dogs. See **Exhibit 10.**

11/2/2011	CVM/FDA	CVM assigned INAD File No. 012-103 for investigational studies for ENTYCE for dogs. See **Exhibit 10.**
11/15/2011	Aratana	Aratana submitted Environmental Assessment (EA) INAD Waiver Request.
11/16/2011	Aratana	Aratana submitted EA NADA Waiver Request.
1/18/2012	Aratana and CVM/FDA	Aratana held educational meeting at CVM/FDA on "Growth Hormone Secretagogues and Ghrelin" presented by Roy G. Smith, Professor and Chair Department of Metabolism and Aging Scripps Florida.
2/22/2012	CVM/FDA	EA INAD Waiver Request Acknowledged.
2/22/2012	CVM/FDA	CVM issued EA NADA Waiver Technical Section Complete Letter (TSCL).
2/29/2012	Aratana	Aratana submitted a PreSubmission Meeting Request.
4/20/2012	Aratana and CVM/FDA	Aratana and CVM/FDA held development conference
5/25/2012	Aratana	Aratana submitted Teleconference Request regarding Effectiveness (EFF) technical section.
6/1/2012	CVM/FDA	CVM issued the Memorandum of Conference (MOC) for the development conference held on April 20, 2012.
6/12/2012	Aratana and CVM/FDA	Aratana and CVM/FDA held EFF teleconference
7/6/2012	CVM/FDA	CVM issued the MOC for the EFF teleconference held on June 12, 2012.
8/6/2012	Aratana	Aratana begins Proof of Concept Clinical Field Study to Evaluate the Effectiveness of AT-002 on Appetite in Dogs (Study No. AT002-CCL-12-001). See **Exhibit 11.**

10/11/2012	Aratana	Aratana submitted Target Animal Safety (TAS) technical section Toxicity Characterization.
1/22/2013	CVM/FDA	CVM issued Response Letter regarding the TAS Toxicity Characterization.
2/12/2013	Aratana	Aratana submitted a PreSubmission Meeting Request regarding EFF and TAS.
3/7/2013	Aratana	Aratana submitted the response to a question raised in the 4/20/2012 development conference regarding the potential for the development of tolerance with chronic use of capromorelin.
4/10/2013	Aratana and CVM/FDA	Aratana and CVM/FDA held EFF and TAS Presubmission Meeting.
4/29/2013	Xenometrics/ Aratana	Aratana begins AT-002 Dose Titration Study in Adult Beagle Dogs Study No. AT-002-CCL-13-002 by Xenometrics for Aratana Therapeutics, Inc. See **Exhibit 12**.
5/9/2013	Aratana	Aratana submitted a Chemistry, Manufacturing and Controls (CMC) PreSubmission Meeting Request.
5/16/2013	Aratana	Aratana submitted justification to use Owner Appetite Assessment as pivotal Effectiveness endpoint.
5/20/2013	CVM/FDA	CVM issued MOC regarding EFF and TAS PreSubmission Meeting held 4/10/2013.
6/6/2013	CVM/FDA	CVM issued a response Letter regarding the 3/7/2013 submission addressing the potential for the development of tolerance with chronic use of capromorelin.
6/17/2013	Aratana and CVM/FDA	Aratana and CVM/FDA held CMC Presubmission Meeting.
6/27/2013	Aratana	Aratana submitted TAS Bioanalytical Method Validation section.

7/31/2013	CVM/FDA	CVM issued the MOC for CMC PreSubmission Meeting held 6/17/2013.
8/1/2013	Aratana	Aratana completed AT-002 Dose Titration Study Number T-002-CCL-13-002. See **Exhibit 13**.
8/23/2013	CVM/FDA	CVM issued Response Letter regarding Owner Appetite Assessment as EFF endpoint.
9/3/2013	Aratana	Aratana submitted TAS Pharmacokinetic Bridging Study Protocol, amended 9/12/2013, 10/30/2013, and 11/7/2013.
9/4/2013	Aratana	Aratana submitted EFF Dog Clinical Field Study Protocol.
10/1/2013	Aratana	Aratana submitted Trade Name Approval Request.
10/3/2013	Aratana	Aratana submitted CMC Stability Protocol, amended 10/31/2013.
10/28/2013	CVM/FDA	CVM issued non-concurrence letter for EFF Dog Clinical Field Study Protocol.
11/8/2013	Aratana	Aratana re-submitted EFF Dog Clinical Field Study Protocol, amended 12/27/2013.
11/8/2013	Aratana	Aratana submitted EFF Dog Food Consumption Study Protocol, amended 1/6/2014.
11/18/2013	CVM/FDA	CVM issued a concurrence regarding the TAS PK Bridging Study Protocol.
11/22/2013	CVM/FDA	CVM issued a concurrence regarding the CMC Stability Protocol.
12/19/2013	CVM/FDA	CVM accepted TAS Bioanalytical Method Validation.
1/2/2014	Aratana	Aratana begins Pivotal Clinical Field Study to Evaluate the Safety and Effectiveness of AT-002 on Stimulation of Appetite in Dogs Study No. AT002-CCL-13-003. See **Exhibit 14.**

1/3/2014	Ricerca/Aratana	Ricerca begins AT-002: Pharmacokinetic Comparison of Two Formulations in a Cross-Over Design in Beagle Dogs for Two Dose Levels Study No. 031599; Aratana Ref. No. AT002-CPK-14-007. See **Exhibit 15.**
1/10/2014	CVM/FDA	CVM Rejected Trade Name Approval Request.
1/14/2014	CVM/FDA	CVM issued concurrence regarding the EFF Dog Clinical Study Protocol.
1/21/2014	CVM/FDA	CVM issued concurrence regarding the EFF Dog Food Consumption Study Protocol.
2/3/2014	Aratana	Aratana submitted a Trade Name Meeting Request.
2/6/2014	Aratana	Aratana submitted TAS 12 Month Oral Toxicity Study.
2/20/2014	Aratana	Aratana completed Proof of Concept Clinical Field Study Number AT002-CCL-12-001. See **Exhibit 11.**
3/11/2014	Aratana and CVM/FDA	Aratana and CVM/FDA conducted Trade Name meeting.
4/18/2014	CVM/FDA	CVM issued MOC regarding TradeName Meeting held 3/11/2014. ENTYCE accepted.
4/30/2014	Aratana	Aratana submitted a CMC PreSubmission Meeting Request.
5/29/2014	Aratana and CVM/FDA	Aratana and CVM/FDA held CMC Presubmission Meeting.
7/9/2014	CVM/FDA	CMC issued MOC regarding PreSubmission Meeting held 5/29/2014.
7/21/2014	Aratana	Aratana submitted EFF Dose Characterization Meeting Request.
7/31/2014	CVM/FDA	CVM accepted TAS 12 Month Oral Toxicity Study.

8/6/2014	Aratana	Aratana completed AT-002: Four Day Repeat Dose Food Consumption Study in Beagle Dogs Study No. 031805; Aratana Ref. No. AT002-CCL-14-004. See **Exhibit 16.**
8/14/2014	Aratana	Aratana completed Pharmacokinetic Comparison Study Number 031599. See **Exhibit 17.**
8/18/2014	Aratana	Aratana submitted a Meeting Request for Interim Blinded Review of cases enrolled to the EFF Clinical Field Study.
8/21/2014	Aratana	Aratana submitted the Capromorelin Veterinary Master File (Capromorelin_VMF).
8/21/2014	Aratana	Aratana submitted a justification for a proposed trifluoroacetic acid (TFA) concentration limit as a residual solvent in Entyce.
8/22/2014	Aratana and CVM/FDA	Aratana and CVM/FDA held EFF Dose Characterization Meeting.
8/22/2014	Aratana	Aratana submitted EFF Food Consumption Study, amended 12/30/2014.
9/17/2014	Aratana	Aratana submitted TAS Pharmacokinetic Bridging Study.
9/26/2014	Aratana and CVM/FDA	Aratana and CVM/FDA held EFF Interim Blinded Review Meeting.
10/3/2014	CVM/FDA	CVM issued MOC regarding EFF Dose Characterization Meeting held 8/22/2014.
11/7/2014	CVM/FDA	CVM issued MOC regarding EFF Interim Blinded Review Meeting held 9/26/2014.
11/14/2014	CVM/FDA	CVM accepted proposed TFA concentration limit as a residual solvent in Entyce.
11/18/2014	Aratana	Aratana submitted EFF Dose Characterization, amended 3/27/2015.

11/26/2014	Aratana	Aratana submitted CMC Technical Section.
2/17/2015	CVM/FDA	CVM accepted EFF Food Consumption Study.
3/9/2015	CVM/FDA	CVM accepted TAS Pharmacokinetic Bridging Study and issued Target Animal Safety Technical Section Complete Letter (TSCL)
4/14/2015	Aratana	Aratana submitted a Meeting Request for Blinded Review of cases enrolled to the EFF Clinical Field Study.
5/22/2015	CVM/FDA	CVM requested additional information to the Capromorelin_VMF.
5/22/2015	CVM/FDA	CVM issued Incomplete Letter regarding CMC Technical Section and offered shortened 60-day resubmission review.
6/25/2015	Aratana and CVM/FDA	Aratana and CVM/FDA held EFF Blinded Review Meeting.
8/4/2015	Aratana	Aratana submitted response to the request for additional information to the Capromorelin_VMF, amended 9/25/2015.
8/4/2015	Aratana	Aratana resubmitted CMC Technical Section, amended 9/9/2015..
8/6/2015	CVM/FDA	CVM issued MOC regarding EFF Blind Rev Meeting held 6/25/2015.
8/25/2015	Aratana	Aratana completed Pivotal Clinical Field Study Number AT002-CCL-13-003. See **Exhibit 14.**
8/26/2015	Aratana	Aratana submitted EFF Clinical Field Study, amended 9/21/2015 and 10/15/2015 to complete the Effectiveness Technical Section.
9/30/2015	CVM/FDA	CVM issued Technical Section Complete Letter (TSCL) regarding CMC Technical Section.
11/12/2015	Aratana	Aratana submitted All Other Information (AOI).

11/12/2015	Aratana	Aratana submitted Labeling, amended 3/14/2016.
2/19/2016	CVM/FDA	CVM accepted EFF Clinical Field Study and issued Effectiveness TSCL.
3/18/2016	CVM/FDA	CVM issued TSCL regarding AOI.
3/18/2016	CVM/FDA	CVM issued TSCL regarding Labeling.
3/18/2016	CVM/FDA	CVM issued the draft Freedom of Information (FOI) summary for the NADA
3/21/2016	Aratana	Aratana submitted the Administrative New Animal Drug Application (NADA) for ENTYCE® for dogs, amended 3/30/2016.
5/16/2016	CVM/FDA	CVM approved NADA No. 141-457 for ENTYCE® for dogs and granted 5 years of marketing exclusivity. See **Exhibit 1**.

Abbreviations:

AOI = All Other Information

CMC = Chemistry, Manufacturing and Controls

EA = Environmental Assessment

EFF = Effectiveness

ERA = End-Review Amendment

FOI = Freedom of Information

INAD = Investigational New Animal Drug

MOC = Memorandum of Conference

TAS = Target Animal Safety

TSCL = Technical Section Complete Letter

VMF = Veterinary Master File

14. Information required by 37 C.F.R. §1.740(a)(12).

Applicant is of the opinion that U.S. Patent No. 6,673,929 is eligible for an extension under 35 U.S.C. §156. Applicant bases this request on 35 U.S.C. §156(c).

More specifically, Applicant believes the extension is justified based on the following information and calculations as required under 37 C.F.R. §1.778:

(1) The statutory term of U.S. Patent No. 6,673,929 expires on February 13, 2020 (twenty years from the filing date (February 1, 2000) plus 12 days of Patent Term Adjustment). The present Application has, therefore, been submitted before the expiration date of the patent term. All maintenance fees have been paid. See **Exhibit 6**.

(2) The term of this patent has never been extended under subsection (e)(1) of U.S.C. §156.

(3) This Application is submitted by RaQualia Pharma Inc., owner of record of the patent, by an Assignment recorded at the U.S. Patent and Trademark Office. See **Exhibit 19**.

(4) This Application is submitted within the sixty-day period beginning on May 16, 2016, that the approved product received permission for commercial marketing or use under the Federal Food, Drug and Cosmetic Act and this application contains the information required under 35. U.S.C. §156(d).

(5) As evidenced by the letter from the FDA dated May 16, 2016 (**Exhibit 1**), the approved product was subject to a regulatory review period under section 512(c)(1) of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use.

(6) The permission for the commercial marketing of the approved product after regulatory review under § 512(c)(1) is the first permitted commercial marketing or use of the approved product.

(7) No other U.S. patent has been extended under subsection (e)(1) of U.S.C. §156.

(8) The total review period, as calculated under 35 U.S.C. §156(g)(4)(B) is the sum of the periods calculated under 35 U.S.C. §156(g)(4)(B)(i) (*i.e.*, the "testing phase") and 35 U.S.C. §156(g)(4)(B)(ii) (*i.e.*, the "approval phase").

(9) The period under 35 U.S.C. §156(g)(4)(B)(i) is 4855 days, *i.e.*, from the December 5, 2002 effective date that major health or environmental effect tests on capromorelin was initiated, to the March 21, 2016 date that NADA No. 141-457 was filed.

(10) The period under 35 U.S.C. §156(g)(4)(B)(ii) is 56 days, *i.e.*, from the March 21, 2016 date that NADA No. 141-457 was filed to the May 16, 2016 date that NADA No. 141-457 was approved. Thus, the total review period is a total of 4855 days and 56 days which totals 4911 days.

(11) A portion of the period under 35 U.S.C. §156(g)(4)(B) occurred before the January 6, 2004 issue date of U.S. Patent No. 6,673,929. Thus, there is a 397 day reduction due to any of the review period occurring before U.S. Patent No. 6,673,929 issued. The reduced total review period is a total of 4514 days. The reduced testing phase is 4458 days.

(12) There is no reduction under 35 U.S.C. §156(c)(1) because it is submitted that Pfizer Inc. and RaQualia Pharma Inc. acted with diligence during the regulatory review period.

(13) As noted above, the reduced testing phase under 35 U.S.C. §156(g)(4)B(i) is 4458 days. Half that period is 2229 days. Thus, the total review period is reduced by 2229 days under 35 U.S.C. §156(c)(2).

(14) After the 35 U.S.C. §156(c)(2) reduction, the qualified review period is 4514 days less 2229 days which totals 2285 days. Thus, U.S. Patent 6,673,929 qualifies for 2285 day term extension.

To summarize:

PTE = RRP – PGRRP – DD – ½(TP-PGTP)

RRP = TP + AP

TP = 4855 days

AP = 56 days

PGRRP = 397 days

DD = 0 days

PGTP = 397 days

PTE = (4855 + 56) – 397 – 0 – ½(4855-397)

PTE = 4911 – 397 – 0 – 2229 = 2285 days

(15) U.S. Patent No. 6,673,929 is set to expire on February 13, 2020. The sum of this term and the 2285 day term extension is May 17, 2026. This extended term does not exceed 14 years added to the date of FDA approval of the approved product on May 16, 2016, i.e. May 16, 2030. The earlier date is May 17, 2026. Accordingly, there is no reduction under 35 U.S.C. §156(c)(3).

(16) U.S. Patent No. 6,673,929 was issued after November 16, 1988. By adding 5 years to the original expiration date, the date obtained is February 13, 2025. By comparing this date with the date obtained in item (15) above, the date of May 17, 2026 obtained in item (15) above, February 13, 2025 is the earlier date. Accordingly, there is a reduction under 35 U.S.C. §156 (g)(6)(A) of 458 days.

(17) Accordingly, the extension for the term of U.S. Patent 6,673,929 should be 1827 days, such that U.S. Patent 6,673,929 will expire on February 13, 2025.

15. Statement required by 37 C.F.R. §1.740(a)(13).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and Secretary of Health and Human Services any information that is material to the determination of the requested extension.

16. Fee required by 37 C.F.R. §1.740(a)(14).

Applicant hereby authorizes the Commissioner to charge Deposit Account No. 23-0975 for the $1,120.00 fee pursuant to 37 C.F.R. §1.20(j) for filing this Application. The Commissioner is hereby authorized to charge any deficient fee(s), or credit any overpayment, to said Deposit Account No. 23-0975.

17. Information required by 37 C.F.R. §1.740(a)(15).

Please address all correspondence regarding this application to:

Warren M. Cheek, PTO Reg. 33,367
Wenderoth, Lind & Ponack, L.L.P.
1030 15th Street, N.W., Suite 400 East
Washington, DC 20005
Tel: (202) 721-8200
Fax: (202) 721-8250

18. Authorized representatives required by 37 C.F.R. §1.730 and MPEP §2752.

A Power of Attorney from the Applicant to the Applicant's undersigned representative is of record in U.S. Patent No. 6,673,929.

19. Pursuant to 37 C.F.R. §1.740(b) and MPEP §2753 (last paragraph).

Submitted herewith are five copies (*i.e.*, an original and 4 additional copies) of this Application to the Patent Office. The Patent Office is requested to call the Applicant's attorney if any issues arise that can be addressed over the telephone.

20. Multiple Applications for Extension of Patent Term of Different Patents for Same Regulatory Review Period.

Pursuant to 37 C.F.R. § 1.785 and MPEP 2761, the Applicant, RaQualia Pharma Inc., has concurrently submitted herewith another application for extension of the patent term of

U.S. Patent No. 6,107,306 for the same approved product, ENTYCE®, for the same regulatory period.

The Office is respectfully requested to consider both applications together and notify the Applicant of the Final Determination for each application simultaneously. Applicant will then elect the patent for which the extension is desired.

Respectfully submitted,

RaQualia Pharma Inc.

By: Warren M Cheek

Attorneys for Applicant
Warren M. Cheek, PTO Reg. 33,367
Robert M. Joynes, PTO Reg. 54,842
Wenderoth, Lind & Ponack, L.L.P.
1030 15th Street, N.W., Suite 400 East
Washington, DC 20005
Tel: (202) 721-8200
Fax: (202) 721-8250

Filing Date: **July 12, 2016**

By Hand Delivery to:

Office of Patent Legal Administration, Room MDW 7D55
600 Dulany Street, Madison Building, Alexandria VA 22314

EXHIBIT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

N-141457-A-0000-OT

Aratana Therapeutics, Inc.
Attention: Bill Zollers, Ph.D.
Vice President – Drug Development
11400 Tomahawk Creek Parkway
Leawood, KS 66211

Re: Request for original approval of ENTYCE

Dear Dr. Zollers:

We approve your original new animal drug application (NADA) for ENTYCE dated March 21, 2016, and amended on March 30, 2016 (M-0002), under section 512(c)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). ENTYCE (capromorelin oral solution) is approved for appetite stimulation in dogs. The expiration dating for this new animal drug is 24 months. We forwarded a notice of this approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this approval according to 21 CFR 514.8. Any change to the conditions of the approval may require the submission of a supplemental application.

ENTYCE, as approved in this letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of this letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application under section 512(b)(1) of the FD&C Act.

Your final printed labeling must be identical to the approved labeling submitted March 21, 2016 (N-141457-A-0000-OT). Please submit a single copy of each component of the final printed labeling before distributing and marketing your new animal drug. If labeling is submitted via eSubmitter, the labeling should be provided in Portable Document Format (.pdf) files, which are an exact electronic representation of the final labeling. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

Under current good manufacturing practice (cGMP) regulations (21 CFR parts 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the product. A product that does not conform to cGMP is adulterated under section 501(a) of the FD&C Act.

If you submit correspondence relating to this approval, your correspondence should reference the date and the principal submission identifier. If you have any questions or comments, please contact Dr. Steven Fleischer, Director, Division of Therapeutic Drugs for Non-Food Animals at (240) 402-0809.

Sincerely,

{see appended electronic signature page}
Tracey H. Forfa, J.D.
Director (Acting)
Center for Veterinary Medicine

Enclosure:
Freedom of Information Summary

Electronic Signature Addendum for Submission ID

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EXHIBIT 2

Date of Approval: May 16, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-457

ENTYCE

capromorelin oral solution

Oral Solution

Dogs

For appetite stimulation in dogs

Sponsored by:

Aratana Therapeutics, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-457

B. Sponsor

Aratana Therapeutics, Inc.
11400 Tomahawk Creek Pkwy
Leawood, Kansas 66211

Drug Labeler Code: 086026

C. Proprietary Name

ENTYCE

D. Product Established Name

Capromorelin oral solution

E. Pharmacological Category

Appetite stimulant

F. Dosage Form

Oral solution

G. Amount of Active Ingredient

30 mg/mL flavored oral solution

H. How Supplied

10 mL, 15 mL, and 30 mL bottles with a measuring syringe

I. Dispensing Status

Rx

J. Dosage Regimen

3 mg/kg once daily

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

ENTYCE (capromorelin oral solution) is indicated for appetite stimulation in dogs.

II. EFFECTIVENESS

ENTYCE is also referred to as AT-002 in the studies below.

A. Dosage Characterization

A dose of 3 mg/kg (1.4 mg/lb; capromorelin as the tartrate salt) of ENTYCE administered orally as a flavored solution once daily for appetite stimulation in dogs was selected based on the following two studies.

1. Adult laboratory Beagle dogs were divided into four groups (3/sex/group; n=6/group). Dogs were dosed orally with a flavored solution for 7 consecutive days. The groups were administered vehicle control (solution minus capromorelin) twice daily (BID), 3 mg/kg capromorelin once daily (SID), 4.5 mg/kg capromorelin SID, or 3 mg/kg capromorelin BID. Dogs were offered more than twice the normal amount of food during both the acclimation (Day -7 to Day -1) and in-life feeding phase (Day 1 to Day 7) of the study. Dogs were fasted overnight and then allowed access to food for 2 hours. Following the 2-hour feeding period, the remaining food was removed from the cage, weighed, and recorded. Baseline food consumption was calculated on Day -3 to Day -1. During the in-life feeding phase, dogs were fed approximately 2 hours post-dose. Dogs were weighed prior to feeding on Days -1, 3, and 7.

   Results: Clinical observations included licking, smacking of the mouth/lips, salivation, and/or grimacing in all groups at dosing.

   Table 1: Change in food consumption and body weight by treatment group.

Capromorelin Dose	Mean Percent Change in Food Consumption from Baseline	P-value[a]	Mean Percent Change in Body Weight from Baseline
0 mg/kg BID	-13.5	N/A	-1.17
3 mg/kg SID	57.72	< 0.0001	4.52
4.5 mg/kg SID	37.91	0.0024	3.78
3 mg/kg BID	36.35	0.0033	4.17

[a] P-value for the difference between vehicle control (0 mg/kg) and each treatment group

   Food consumption was statistically significantly increased in all groups administered capromorelin when compared to the vehicle control group. The percent change in body weight was greater in the capromorelin groups compared to the vehicle control group.

2. Adult laboratory Beagle dogs were divided into five groups (3/sex/group; n=6/group). Dogs were dosed orally once daily for 7 consecutive days. The groups were administered vehicle control (solution minus capromorelin), 0.33, 2, 3, or 4 mg/kg capromorelin. The capromorelin test article was the final flavored oral solution formulation proposed for marketing. Dogs were offered more than twice the normal amount of food during both the acclimation (Day -10 to Day -1) and in-life feeding phase (Day 1 to Day 7) of the study. Dogs

were fasted overnight and then allowed access to food for 2 hours. Following the 2-hour feeding period, the remaining food was removed from the cage and weighed. Baseline food consumption was calculated on Day -3 to Day -1. During the in-life feeding phase, dogs were fed approximately 2 hours post-dose. Dogs were weighed prior to feeding on Days -10, -7, -1, 1, and 8. The percent change in food consumption from baseline compared to the treatment period (average of Day 1 through Day 7) was calculated for each dog.

Results: Clinical observations included salivation and head shaking in all groups at dosing.

Table 2 summarizes the analysis results for food consumption. The 2, 3, and 4 mg/kg capromorelin groups showed statistically significant increased food consumption when compared to the vehicle control group.

Table 2: Change in food consumption by treatment group.

Capromorelin Dose (Once daily)	**Mean Percent Change in Food consumption from Baseline**	**P-value[a]**
0 mg/kg	2.44	N/A
0.33 mg/kg	28.74	0.0879
2 mg/kg	38.92	0.0217
3 mg/kg	33.74	0.0452
4 mg/kg	64.10	0.0004

[a] P-value for the difference between vehicle control (0 mg/kg) and each treatment group

Table 3 summarizes the analysis results for body weight. Body weight increased in females and males in all capromorelin treatment groups.

Table 3: Change in body weight by gender and treatment group.

Capromorelin Dose (Once daily)	**Mean Percent Change in Body Weight from Baseline (in Females, Males)**
0 mg/kg	0.46, -0.37
0.33 mg/kg	2.65, 1.06
2 mg/kg	3.27, 6.63
3 mg/kg	6.25, 4.44
4 mg/kg	2.97, 6.97

B. Substantial Evidence

1. Laboratory Study:

   a. Title: AT-002: Four-day repeat dose food consumption study in Beagle dogs. Study #031805

   b. Study Location: Concord, OH

   c. Study Design:

      (i) Objective: To determine and compare food intake over a 4-day period of daily oral administration of ENTYCE (capromorelin oral solution) and a vehicle control.

      (ii) Study Animals: The study included 24 healthy Beagle dogs, approximately 13-14 months old at first dose administration. The body weights were approximately 6.5 to 9 kg for females and 10 to 12.5 kg for males at the time of randomization.

      (iii) Control and treatment groups:

      Table 4: Treatment groups:

Treatment Group	Dose (mg/kg)	No. and Gender of Dogs
Group 1	0 mg/kg	6 males and 6 females
Group 2	3 mg/kg (1X)	6 males and 6 females

      (iv) Dosage form: The capromorelin was formulated in a flavored oral solution. The vehicle control solution was the identical solution minus active pharmaceutical ingredient.

      (v) Route of administration: Oral

      (vi) Dosage amount, frequency, and duration: ENTYCE or vehicle control was administered once daily for 4 consecutive days. Dogs were fasted at the time of administration. Dosages on all dosing days were calculated for each dog, based on body weights from Day 0 (first day of treatment).

      (vii) Measurements and Observations: Clinical observations, body weight, food consumption, physical examination, complete blood count (CBC), and serum chemistry were performed. Food consumption was measured daily for each dog from Day -14 to Day 3. Dogs were offered more than twice the normal amount of food during both the acclimation (Day -14 to Day -1) and in-life feeding phase (Day 0 to Day 3). Dogs were fasted overnight and then allowed access to food for 3 hours. Following the 3-hour feeding period, the remaining food was removed from the cage, weighed, and recorded. Baseline food consumption was calculated on Day -3 to Day -1. During the in-life phase, dogs were fed approximately 1 hour post-dose.

(viii) Statistical Methods: Percent change from baseline body weight and food consumption was modeled by analysis of variance including treatment, sex, and the treatment-by-sex interaction as fixed effects. If the interaction term was statistically significant then the treatment group comparisons were carried out for each sex separately. Also, within treatment group, comparisons were assessed by the one-sample t-test or Wilcoxon signed rank test, as determined to be appropriate by the Shapiro-Wilk test for normality, to evaluate the percent change from baseline for body weight and food consumption.

d. Results:

Salivation was observed repeatedly in six dogs in the ENTYCE group post-dosing during all treatment days and in two dogs administered vehicle control only one time on Day 0. Emesis was observed in one dog in the ENTYCE group one hour after dosing on Day 1. There were no treatment related findings in the clinical pathology and physical examination results.

The percent change in food consumption was statistically significantly greater ($p<0.001$) in the ENTYCE group (pooled sexes mean = 60.55% change, corresponding to an average 117.6 gram increase in daily consumption) when compared to the vehicle control group (pooled sexes mean = -11.15% change, corresponding to an average 30.4 gram decrease in daily consumption).

The percent change in body weight was greater in the ENTYCE group (5.963%; corresponding to an average 0.52 kg gain) compared to the vehicle control group (0.0532% change; corresponding to an average 0.004 kg gain).

e. Conclusions:

This study supports the effectiveness of ENTYCE as an appetite stimulant in dogs. ENTYCE administered orally once a day at a dose of 3 mg/kg/day for 4 consecutive days to approximately 13-14 month old Beagle dogs (6/sex/group) was associated with increased food consumption and body weight.

2. Field Study:

a. Title: Pivotal clinical field study to evaluate the safety and effectiveness of AT-002 on stimulation of appetite in dogs. Study #AT002-CCL-13-003

b. Study Locations:

Riverside, CA	West Palm Beach, FL	Ralston, NE
Los Angeles, CA	Bradenton, FL	Bedford Hills, NY
Fort Collins, CO	Bartonville, IL	Norristown, PA
Denver, CO	Lawrence, KS	Quakertown, PA
Fort Collins, CO	Overland Park, KS	Collierville, TN
Gainesville, FL	Canton, MI	Dallas, TX
Ocala, FL	Grand Rapids, MI	Sequin, TX
West Palm Beach, FL	Springfield, MO	Antioch, TX

c. Study Design:

(i) Objective: To confirm the safety and effectiveness of ENTYCE in dogs under field conditions using a dose of 3 mg/kg administered once daily. The study was conducted according to Good Clinical Practice (GCP).

(ii) Study animals: Two hundred forty-four (244) dogs were enrolled in the study and received at least one treatment. Age of the enrolled dogs ranged from 0.3 to 18.0 years and body weights ranged between 1.5 and 76.6 kilograms at the start of treatment. One hundred twenty-two (122) female dogs were enrolled, 12 of which were intact. One hundred twenty-two (122) males were enrolled, 26 of which were intact. The enrolled dogs had various medical conditions at day 0: arthritis (40); gastrointestinal disease (24); allergy (22); dental disease (22); cardiovascular disease (16); renal disease (13); and others.

(iii) Inclusion criteria:
- Dogs presented with a reduced appetite or no appetite for a minimum of 2 days prior to day 0
- Owner Appetite Assessment score at screening of "Decreased"
- Dogs on medications for certain chronic conditions (such as osteoarthritis, hypothyroidism) were included as long as in the Investigator's/Examining Veterinarian's opinion, the medical condition, treatment regimen and clinical condition was stable

(iv) Exclusion criteria:
- Intended for breeding, or pregnant or lactating female dogs
- Dogs in crisis or moribund
- At the Investigator's discretion, a dog with a serious deteriorating condition and/or preliminary laboratory testing results indicating a condition that was serious and/or life threatening
- Dogs hospitalized within the last 4 days
- Dogs with an active infection (e.g. gastroenteritis) that would respond to standard of care, such as treatment with antibiotics
- Dogs in which food intake was contraindicated (i.e. suspected foreign body, gastric torsion, gastrointestinal surgery)
- Dogs with a regurgitation problem
- Dogs with dental disease severe enough to impair food intake

- Dogs with diabetes
- Any dog where the Owner is unsure that they can reliably evaluate the appetite (e.g. multi-pet household)
- Dogs currently receiving prohibited medications

(v) Treatment and Vehicle Control Groups: Dogs were randomly assigned into two treatment groups in a 2:1 ratio of ENTYCE oral solution or vehicle control (solution minus capromorelin). Veterinarians and owners were masked to treatment group assignment.

Table 5: Treatment groups:

Treatment Group	Dose (mg/kg)	Number of Dogs
ENTYCE oral solution	3 mg/kg	171
Vehicle Control	0 mg/kg	73

(vi) Drug administration: Dogs were administered ENTYCE oral solution at 3 mg/kg or a matched vehicle control oral solution once daily for 4±1 days.

(vii) Measurements and Observations: The primary effectiveness endpoint was an owner appetite assessment at day 3±1. Owners were asked to rate their dog's appetite as "increased", "no change", or "decreased". On day 0 (prior to the first dose), the owner must score their dog as "decreased" to be enrolled on the study. On day 3±1, if the owner scored their dog as "increased" this was considered a treatment success. On day 3±1, if the owner scored their dog as "no change" or "decreased" this was considered a treatment failure.

A secondary effectiveness variable was an owner appetite assessment questionnaire completed on day 0 (prior to the first dose) and day 3±1. Owners were asked to rate five questions about their dog's appetite. Each question was worth 1 to 5 points for a total score of 5 to 25 points. Treatment success was defined as an "increase in total score of 5 points or more from day 0 to day 3±1". The treatment success was defined as an "increase in total score of 5 points or more from day 0 to day 3±1".

A secondary effectiveness variable was body weight. Treatment success was defined as "more than a zero percent increase in body weight from day 0 to day 3±1".

Safety was assessed through adverse reactions, clinical pathology, and physical examinations.

(viii) Statistical Methods: The analyses of the effectiveness parameters were conducted on a per protocol population, which comprised those dogs without significant protocol violations or missing assessments.

The primary effectiveness variable (owner appetite assessment) was the percent success rate at day 3±1. The primary effectiveness variable (treatment success or failure) was analyzed using a generalized linear mixed model assuming a binomial distribution and

using a logit link. The model included treatment group as a fixed effect, and site and treatment by site interaction as random effects. A 95% confidence interval was calculated for the difference in success rates between active group and vehicle control.

Secondary outcome variables (owner appetite assessment questionnaire and body weight) included success rates and were presented and analyzed as described for the primary outcome variable. Secondary outcome variables also included the percent changes from day 0 to day 3±1. Analysis of variance modeling was employed to assess possible differences between treatment groups. The model contained terms for treatment, site and treatment by site interaction.

d. Results:

(i) Primary effectiveness: Effectiveness was evaluated by owner appetite assessment in 177 dogs; 121 dogs in the ENTYCE oral solution group and 56 dogs in the vehicle control group.

Table 6: Owner Appetite Assessment: Observed success rate on day 3±1 compared to Day 0

Success/Failure	**ENTYCE oral solution (N=121)**	**Vehicle Control (N=56)**
Success	83 (68.6%)	25 (44.6%)
Failure	38 (31.4%)	31 (55.4%)

Based on the statistical model, the estimated success rates are 67.9% and 42.6% for the ENTYCE group and the vehicle control groups, respectively. The difference in success rates is significant at P=0.0078.

(ii) Secondary effectiveness variables:

(a) Owner appetite assessment questionnaire: With success defined as an increase in the total score by 5 points or more from day 0 to day 3±1, a success rate observed in the ENTYCE oral solution group was 56.2% compared to the vehicle control group 26.8%.

Table 7: Owner Appetite Assessment Questionnaire: Observed success rate on day 3±1 compared to day 0

Success/Failure	**ENTYCE oral solution (N=121)**	**Vehicle Control (N=56)**
Success	68 (56.2%)	15 (26.8%)
Failure	53 (43.8%)	41 (73.2%)

(b) Body weight: The mean percent change (±SD) from day 0 to day 3±1 was 1.83% (±2.75) for the ENTYCE oral solution group and 0.11% (±3.61) for the vehicle control group.

Table 8: Body Weight: Percent change in body weight on Day 3±1 compared to day 0

Percent Change in Body Weight	ENTYCE oral solution (N=121)	Vehicle Control (N=56)
>0%	92 (76.0%)	25 (44.6%)
≤0%	29 (24.0%)	32 (55.4%)

e. Adverse Reactions:

All dogs (n=244; 171 administered ENTYCE, 73 administered vehicle control) enrolled in the study were evaluated for adverse reactions. The enrolled dogs had decreased appetite due to various medical conditions. Some dogs may have experienced more than one of the adverse reactions during the study. The following adverse reactions were observed.

Table 9: Adverse Reactions reported in dogs administered ENTYCE oral solution compared to Vehicle Control

Organ System	Adverse Reaction	ENTYCE oral solution (N=171) n (%)	Vehicle Control (N=73) n (%)
Gastrointestinal	Diarrhea	12 (7.0 %)	5 (6.8 %)
	Vomiting	11 (6.4 %)	4 (5.5 %)
	Hypersalivation	4 (2.3 %)	0 (0.0 %)
	Abdominal discomfort	2 (1.2 %)	0 (0.0 %)
	Flatulence	2 (1.2 %)	0 (0.0 %)
	Nausea	2 (1.2 %)	0 (0.0 %)
Clinical Pathology	Elevated blood urea nitrogen	7 (4.1 %)	2 (2.7 %)
	Elevated phosphorus	4 (2.3 %)	1 (1.4 %)
	Elevated creatinine	1 (0.6 %)	1 (1.4 %)
Other	Polydipsia	7 (4.1 %)	1 (1.4 %)
	Lethargy/depression	2 (1.2 %)	0 (0.0 %)

The following adverse reactions were reported in <1% of dogs administered ENTYCE: hyperactivity, increase fecal volume, increase gut sounds, and polyuria.

f. Conclusions: Administration of ENTYCE oral solution at a dose of 3 mg/kg once daily for 4 days was safe and effective for appetite stimulation in dogs.

III. TARGET ANIMAL SAFETY

A. Safety Study:

1. Title: CP-424,391-18 – 1 Year Oral Toxicity Study in Beagle Dogs. Study #96-1340-13.

2. Study Location: Groton, CT

3. Study Design:

   a. Objective: To investigate the potential toxicity of CP-424,391-18 (also known as capromorelin) in Beagle dogs following oral administration, once daily, for 12-months at 0 (placebo), 0.3, 7, and 40 mg/kg/day.

   b. Study Animals: Thirty-two healthy Beagle dogs, approximately 11-12 months old at first dose administration, weighing 9-13.6 kg.

   c. Control and treatment groups:

   Table 10: Treatment groups:

Tx Group	Dose (mg/kg)	Number and Gender of Dogs
Group 1	0 mg/kg	4 males and 4 females
Group 2	0.3 mg/kg (0.13X)	4 males and 4 females
Group 3	7 mg/kg (3.07X)	4 males and 4 females
Group 4	40 mg/kg (17.5 X)	4 males and 4 females

   Note: The 0.3, 7, and 40 mg/kg doses are based on capromorelin base. The equivalent doses based on capromorelin tartrate were 0.39, 9.2 and 52.4 mg/kg. The therapeutic dose is 3 mg/kg based on capromorelin tartrate.

   d. Dosage form: The active pharmaceutical ingredient was dissolved in deionized water. This formulation was not the final market formulation.

   e. Route of administration: Oral gavage

   f. Dosage amount, frequency, and duration: Capromorelin was administered once daily for 12 consecutive months. Dogs were fasted at the time of administration.

   g. Measurements and Observations: Clinical observations, body weight, food consumption, physical examination/vital signs, electrocardiogram, blood pressure, ophthalmology examination, complete blood count (CBC) and serum chemistry, urinalysis, capromorelin plasma concentration, growth hormone (GH) and insulin-like growth factor-1 plasma concentrations, gross pathology, organ weights, and histopathology were performed.

h. Statistical Methods: Models included treatment, sex, and the treatment-by-sex interaction as fixed effects. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time, and treatment-by-sex-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate.

4. Results:

Administration of capromorelin was associated with increased salivation and reddening/swollen paws. No treatment related clinical effects were noted on vital signs. No treatment related effects were noted on ophthalmology examinations. Electrocardiograms noted an increase in the PRQ interval at 1 to 2 hours post-dose in the 7 mg/kg/day and 40 mg/kg/day groups. No histological lesions were observed in the heart. There were treatment related decreases in red blood cell count, hemoglobin, and hematocrit in the 40 mg/kg group. Pale skin, pale gums, and decreased red blood cell count, hemoglobin and hematocrit were observed in one dog administered 40 mg/kg/day. Increases were noted in cholesterol, high density lipoproteins, and the liver specific isozyme of serum alkaline phosphatase (ALP) in the 40 mg/kg group. Growth hormone and insulin like growth factor-1 (IGF-1) plasma levels were increased in all groups administered capromorelin. Liver weights were increased in the 7 mg/kg/day and 40 mg/kg/day groups. An increase in hepatocellular cytoplasmic vacuolation was observed in all groups. There were no effects noted on gross necropsy. Capromorelin levels were similar in plasma collected on days 90, 181, and 349 indicating no accumulation of the drug.

5. Conclusions:

This study supports the safe use of capromorelin administered orally at 3 mg/kg/day. Oral administration of capromorelin via oral gavage to approximately 11-12 month old Beagle dogs (4/sex/dose) at doses of 0, 0.3, 7, and 40 mg/kg/day for 12 consecutive months was associated with increased salivation, reddening/swollen paws, increased liver weights, and hepatocellular cytoplasmic vacuolation. Other findings considered to be related to the oral administration of capromorelin at the 40 mg/kg group include decreased red blood cell count, hemoglobin, and hematocrit; and increased ALP, cholesterol, high density lipoproteins, GH, and IGF-1.

B. Pharmacokinetic Study:

1. Title: AT-002: Pharmacokinetic comparison of two formulations in a cross-over design in Beagle dogs for two dose levels. Study #031599

2. Study Location: Concord, OH

3. Study Design:

   a. Objective: To investigate and compare the pharmacokinetic (PK) parameters of capromorelin after a single oral administration of ENTYCE (capromorelin oral solution) and a deionized water formulation, at two dose levels (3 mg/kg and 52.4 mg/kg), in a crossover study design in Beagle dogs.

   b. Study Animals: The study included 24 healthy Beagle dogs, approximately 12 months old at first dose administration, weighing between 6.2 and 12.3 kg. To control for bias, animals were randomly assigned to Groups 1A-2B, using a computer-generated randomization procedure based on body weight.

   c. Treatment Groups:

Table 11: Treatment groups:

Tx Group	Dose (mg/kg)	Animal Cohort	Day 0 Formulation	Day 7 Formulation	Number and Gender of Animals
Group 1	3	A	ENTYCE	Deionized	3 males and 3 females
	3	B	Deionized	ENTYCE	3 males and 3 females
Group 2	52.4	A	ENTYCE	Deionized	3 males and 3 females
	52.4	B	Deionized	ENTYCE	3 males and 3 females

   d. Dosage form: The study evaluated two different formulations. In the "deionized" formulation, the active pharmaceutical ingredient (API) was dissolved in deionized water. In the "flavored" formulation, the active pharmaceutical ingredient was in an oral flavored solution. This flavored solution is the final market formulation (ENTYCE).

   e. Route of administration: Oral gavage

   f. Dosage amount, frequency, and duration: Dogs received a single dose of each formulation of capromorelin with a 7-day washout period between dose administrations. Dosing occurred following an overnight fast. Food was offered approximately 4 hours post-dose.

   g. Measurements and Observations: Clinical observations, physical examination, hematology, serum chemistry, body weight measurement, and capromorelin serum concentration were performed.

h. Following dosing on Days 0 and 7, blood samples were collected in tubes without anticoagulant from all animals pre-dose and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose. Serum was harvested for analysis of capromorelin concentration. Non-compartmental PK parameters as defined below were calculated.

- $AUC_{(0\text{-}t)}$ =Area under the time vs. capromorelin serum concentration curve from time 0 to last measurable concentrations (t_{last})
- C_{max}=Peak capromorelin serum concentration
- T_{max}=Time to reach peak capromorelin serum concentration
- $T_{1/2}$ = Terminal elimination half-life
- $AUC_{(0\text{-}inf)}$ = Area under the time vs. capromorelin serum concentration curve from time 0 to infinity calculated as sum of $AUC_{(0\text{-}t)}$ and (t_{last}/terminal elimination rate constant).

i. Statistical Methods: An analysis of variance (ANOVA) was conducted to assess formulation differences for each dose of C_{max}, T_{max}, and $AUC_{(0\text{-}t)}$ and to determine the intrasubject coefficient of variation. For each dose, the PK parameters were natural log-transformed, and the ANOVA model included sequence, formulation and period as fixed effects, with the subject nested within sequence as a random effect. Each ANOVA included calculation of least square mean (LSM), the difference between formulation LSM, and the standard error associated with the difference for each dose. Ratios of LSM were calculated for each dose using C_{max}, T_{max}, and $AUC_{(0\text{-}t)}$. For each dose, these ratios were expressed as a percentage relative to the reference formulation (deionized water). Ninety percent confidence intervals for the ratios were derived for each dose. If a dog vomited within the first hour of dosing on any dose day, the statistical analysis for that day was performed with and without that dog.

4. Results:

A relative bioavailability analysis was performed using data from all dogs (n=12) administered 3 mg capromorelin/kg bodyweight. Dogs administered 3 mg/kg of ENTYCE had a lower capromorelin exposure than the dogs administered 3 mg/kg of the API in deionized water (relative bioavailability based on geometric mean $AUC_{(0\text{-}t)}$ ratio of 74.4% with 90% CI: 61.12 to 90.57). Further, the capromorelin C_{max} was lower following administration of ENTYCE compared to following administration of the API in deionized water (geometric mean C_{max} ratio of 83.07% with 90% CI: 64.20 to 107.5). At the 3 mg/kg dose, the median T_{max} and mean terminal half-life following both the formulations was similar (0.5 hr and ~1 hr respectively).

Table 12: Summary of Statistical Analysis Including All Dogs (Dose = 3 mg/kg)

Parameter	Geometric Mean (Deionized)	Geometric Mean (ENTYCE)	Ratio% (ENTYCE/Deionized)	90% CI	P-value
$AUC_{(0-t)}$ (hr*ng/mL)	793.88	590.68	74.40	(61.12, 90.57)	0.0214
C_{max} (ng/mL)	360.96	299.84	83.07	(64.20, 107.5)	0.2212
T_{max} (hr)	0.67	0.71	105.9	(68.12, 164.8)	0.8174

$AUC_{(0-t)}$ =Area under the time vs. capromorelin serum concentration curve from time 0 to last measurable concentrations
C_{max}=Peak capromorelin serum concentration
T_{max}=Time to reach peak capromorelin serum concentration
CI= Confidence intervals

At the 52.4 mg/kg dose level, there were a number of dogs in both groups (9 dogs in the Deionized group and 6 dogs in ENTYCE group) that had episodes of emesis within 0.5 hr after dose administration. The observed median T_{max} at the 52.4 mg/kg dose was within 0.5 hr (range 0.5-2 hr). Because one or more emetic events occurred prior to C_{max}, the dogs could be considered to have missed the dose. Although a small number of dogs (3 dogs in Deionized group and 6 dogs in ENTYCE group) provided evaluable PK data at 52.4 mg/kg dose, the relative bioavailability for the 52.4 mg/kg dose was not calculated as there were not sufficient dogs without emesis to perform any inferential ANOVA analysis.

5. Conclusions:

This PK study adequately bridges the exposure of ENTYCE to the exposure of capromorelin in deionized water, as was used in the 1-Year Oral Toxicity Study in Beagle Dogs (#96-1340-13), for the purpose of assessing target animal safety. This PK study showed that a 3 mg/kg dose of ENTYCE results in lower capromorelin exposure than that of capromorelin in deionized water. Further, the capromorelin C_{max} was lower following administration of ENTYCE compared to capromorelin in deionized water (geometric mean C_{max} ratio of 83.07% with 90% CI: 64.20 to 107.5). Therefore drug exposure in the 1-Year Oral Toxicity Study in Beagle Dogs is representative for evaluating the margin of safety for the flavored oral solution formulation.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ENTYCE:

> "Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans. **For use in dogs only."**

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that ENTYCE, when used according to the label, is safe and effective for appetite stimulation in dogs.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed to diagnose and manage decreased appetite in dogs. Furthermore, the veterinarians' expertise is needed to monitor patients for possible adverse effects of the drug.

B. Exclusivity

ENTYCE as approved in our approval letter qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.

EXHIBIT 3

entyce®

(capromorelin oral solution)

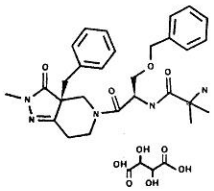
30 mg/mL

For oral use in dogs only

Appetite Stimulant

Caution:
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
ENTYCE® (capromorelin oral solution) is a selective ghrelin receptor agonist that binds to receptors and affects signaling in the hypothalamus to cause appetite stimulation and binds to the growth hormone secretagogue receptor in the pituitary gland to increase growth hormone secretion. The empirical formula is $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_6$ and the molecular weight 655.70. The chemical name is 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartrate.



The chemical structure of capromorelin tartrate is:

Indication:
ENTYCE (capromorelin oral solution) is indicated for appetite stimulation in dogs.

Dosage and Administration:
Administer ENTYCE orally at a dose of 3 mg/kg (1.4 mg/lb) body weight once daily.

To administer ENTYCE, gently shake the bottle, and then withdraw the appropriate amount of solution using the provided syringe. Rinse syringe between treatment doses.

The effectiveness of ENTYCE has not been evaluated beyond 4 days of treatment in the clinical field study (See Effectiveness).

Contraindications:
ENTYCE should not be used in dogs that have a hypersensitivity to capromorelin.

Warnings:
Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans. **For use in dogs only**

Precautions:
Use with caution in dogs with hepatic dysfunction. ENTYCE is metabolized by CYP3A4 and CYP3A5 enzymes (See Clinical Pharmacology).

Use with caution in dogs with renal insufficiency. ENTYCE is excreted approximately 37% in urine and 62% in feces (See Adverse Reactions and Clinical Pharmacology).

The safe use of ENTYCE has not been evaluated in dogs used for breeding or pregnant or lactating bitches.

Adverse Reactions:
In a controlled field study, 244 dogs were evaluated for safety when administered either ENTYCE or a vehicle control (solution minus capromorelin) at a dose of 3 mg/kg once daily for 4 days. Enrolled dogs had a reduced or absent appetite for a minimum of 2 days prior to day 0 and had various medical conditions: arthritis (40); gastrointestinal disease (24); allergy (22); dental disease (22); cardiovascular disease (16); renal disease (13); and others. Some dogs may have experienced more than one of the adverse reactions during the study. The following adverse reactions were observed:

Table 1: Adverse Reactions reported in dogs administered ENTYCE oral solution compared to vehicle control

Adverse Reactions	ENTYCE (n = 171) n (%)	Vehicle Control (n = 73) n (%)
GASTROINTESTINAL		
Diarrhea	12 (7.0 %)	5 (6.8 %)
Vomiting	11 (6.4 %)	4 (5.5 %)
Hypersalivation	4 (2.3 %)	0 (0.0 %)
Abdominal discomfort	2 (1.2 %)	0 (0.0 %)
Flatulence	2 (1.2 %)	0 (0.0 %)
Nausea	2 (1.2 %)	0 (0.0 %)
CLINICAL PATHOLOGY		
Elevated blood urea nitrogen	7 (4.1 %)	2 (2.7 %)
Elevated phosphorus	4 (2.3 %)	1 (1.4 %)
Elevated creatinine	1 (0.6 %)	1 (1.4 %)
OTHER		
Polydipsia	7 (4.1 %)	1 (1.4 %)
Lethargy/depression	2 (1.2 %)	0 (0.0 %)

The following adverse reactions were reported in < 1% of dogs administered ENTYCE: hyperactivity, increase fecal volume, increase gut sounds, and polyuria.

To report suspected adverse drug events and/or to obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, call Aratana Therapeutics at 1-844-272-8262.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or at http://www.fda.gov/AnimalVeterinary/SafetyHealth

(continued on other side)

Clinical Pharmacology:

Following oral administration of ENTYCE at a dose of 3 mg/kg to 12 Beagle dogs, absorption of capromorelin was rapid with the maximum concentration (C_{max}) reached within 0.83 hr (T_{max}). After C_{max}, the plasma concentrations declined mono-exponentially with a short terminal half-life ($T_{½}$) of approximately 1.19 hrs. There were no gender differences in capromorelin pharmacokinetics. The exposure (C_{max} and AUC) of capromorelin increased with dose, but the increases were not dose proportional following single and repeat once daily administrations of capromorelin. There was no drug accumulation following repeat oral administration.

Table 2. Plasma PK parameters following oral administration of 3 mg/kg of ENTYCE

Parameter	Mean	SD
T_{max} (hr)	0.83	0.58
C_{max} (ng/mL)	330	143
AUC_t (ng*hr/mL)	655	276
AUC_{inf} (ng*hr/mL)	695	262
$T_{½}$ (hr)	1.19	0.17

The mean absolute oral bioavailability of capromorelin was 44%. The mean total plasma clearance and volume of distribution was 18.9 mL/min/kg and 2.0 L/kg, respectively. Capromorelin was not highly bound (unbound fraction 51%) to plasma protein. The protein binding was concentration-independent over the range of 10 to 1000 ng/mL. *In vitro* (human liver microsomes) and *in vivo* (rats) metabolism studies suggest that capromorelin is metabolized by hepatic enzymes, mainly CYP3A4 and CYP3A5. Therefore, drugs that inhibit CYP3A4 and CYP3A5 activity may affect capromorelin metabolism. Following oral administration of radio-labelled capromorelin to dogs, capromorelin was excreted in urine (37%) and in feces (62%) within 72 hours.

Effectiveness:

Laboratory Effectiveness Study: Twenty four healthy Beagle dogs (6 dogs per sex in each group) with normal appetite were randomized into two groups and dosed daily with ENTYCE (capromorelin oral solution) at 3 mg/kg/day or vehicle control (solution minus capromorelin) to compare food intake over a 4-day period. The dogs were 13 months of age and weighed between 6.5 and 12.5 kg at the time of randomization. Six dogs administered ENTYCE repeatedly exhibited salivation post dosing and two dogs administered vehicle control exhibited salivation only one time on study day 0. Emesis was observed in one dog administered ENTYCE on study day 1. Dogs administered ENTYCE at a dose of 3 mg/kg/day for 4 consecutive days had statistically significantly increased food consumption compared to the vehicle control group ($p < 0.001$).

Clinical Field Study: Effectiveness was evaluated in 177 dogs (121 dogs in the ENTYCE group and 56 dogs in the vehicle control group) in a double-masked, vehicle controlled field study. Dogs with a reduced appetite or no appetite, with various medical conditions, for a minimum of 2 days prior to day 0 were enrolled in the study. The dogs ranged in age from 4 months to 18 years. Dogs were randomized to treatment group and dosed once daily for 4 days with ENTYCE at 3 mg/kg or vehicle control. Dogs were assessed for appetite by owners on day 0 and day 3 ± 1 using an "increased", "no change" or "decreased" scoring system. Dogs were classified as a treatment success if the owner scored their dog's appetite as "increased" on day 3 ± 1. The success rates of the two groups were significantly different ($p = 0.0078$); 68.6% (n = 83) of dogs administered ENTYCE were successes, compared to 44.6% (n = 25) of the dogs in the vehicle control group.

Animal Safety:

In a 12-month laboratory safety study, 32 healthy Beagle dogs (4 dogs per sex per group) approximately 11-12 months of age and weighing 9-13.6 kg were dosed orally with capromorelin in deionized water daily at 0X (placebo), 0.3 (0.13X), 7 (3.07X), and 40 (17.5X) mg/kg/day. Administration of capromorelin was associated with increased salivation and reddening/swollen paws, increased liver weights and hepatocellular cytoplasmic vacuolation. Treatment related decreases were seen in red blood cell count, hemoglobin and hematocrit in the 40 mg/kg group. Pale skin, pale gums, and decreased red blood cell count, hemoglobin and hematocrit were observed in one dog administered 40 mg/kg/day. Increases were seen in cholesterol, high density lipoproteins, and the liver specific isozyme of serum alkaline phosphatase in the 40 mg/kg group. Growth hormone and insulin-like growth factor 1 plasma levels were increased in all groups administered capromorelin. There were no effects noted on gross necropsy. Capromorelin levels were similar in plasma collected on days 90, 181, and 349 indicating no accumulation of drug.

Storage Conditions:

Store at or below 86° F (30° C)

How Supplied:

30 mg/mL flavored solution in 10 mL, 15 mL and 30 mL bottles with measuring syringe

NADA 141-457, Approved by FDA

US Patent: 6,673,929

Made in New Zealand

ARATANA THERAPEUTICS

Manufactured for:
Aratana Therapeutics, Inc.
Leawood, KS 66211

AT2-015-1S
March 2016

EXHIBIT 4

ARATANA THERAPEUTICS

11420 Tomahawk Creek Pkwy, Suite 340, Leawood, KS 66211
Phone: 1-(844) 272-8262 Fax: (913) 904-9641

www.aratana.com

June 22, 2016
RAQUALIA PHARMA INC.
1-21-19 Meieki Minami, Nakamura-ku,
Nagoya-shi, Aichi, 450-0003
Japan

Re: Patent Term Extension Application
U.S. Patent Nos. 6,673,929 and 6,107,306
ENTYCE ®
NADA 141-457

To Whom It May Concern:

Per your request, I hereby confirm that Aratana Therapeutics, Inc. (Aratana) is the Marketing Applicant for ENTYCE® with the U.S. Food and Drug Administration's Center for Veterinary Medicine (FDA). Aratana and RaQualia Pharma Inc. (RaQualia) are parties to an Exclusive IP License Agreement, dated December 27, 2010, that includes the right, among other things, to develop, manufacture, market and/or sell certain RaQualia patented technology, including the branded and now FDA-approved product ENTYCE® (capromorelin oral solution) for appetite stimulation in dogs.

We authorize RaQualia to rely upon our activities before the FDA in connection with ENTYCE® solely for requesting a patent term extension of the U.S. Patent Nos. 6,673,929 and 6,107,306 during the entire regulatory review period of Aratana's activities.

Such activities include:

(1) Aratana's submissions and correspondence with the FDA in INAD No. 012-103 filed on November 1, 2011;

(2) Aratana's activities as Sponsor in connection with animal studies beginning on August 6, 2012, and ending on August 25, 2015; and

(3) Aratana's submissions and correspondence with the FDA in NADA 141-457 filed on March 21, 2016, and approved on May 16, 2016.

Should you have any questions or need further documentation, please do not hesitate to contact us at +1 913-353-1006.

Very truly yours,
ARATANA THERAPEUTICS, INC.

By: _____
Name: Ernst Heinen
Title: Chief Development Officer
Date: 22 June 2016

EXHIBIT 5

US006673929B2

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

(10) **Patent No.: US 6,673,929 B2**
(45) **Date of Patent: Jan. 6, 2004**

(54) **PROCESS FOR PREPARING GROWTH HORMONE SECRETAGOGUES**

(75) Inventors: **Frank R. Busch**, Gales Ferry, CT (US); **Charles K. Chiu**, Guilford, CT (US); **Clifford N. Meltz**, Niantic, CT (US); **Ronald J. Post**, Mystic, CT (US); **Peter R. Rose**, Ledyard, CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 12 days.

(21) Appl. No.: **10/283,720**

(22) Filed: **Oct. 30, 2002**

(65) **Prior Publication Data**

US 2003/0158414 A1 Aug. 21, 2003

Related U.S. Application Data

(62) Division of application No. 09/496,075, filed on Feb. 1, 2000, now Pat. No. 6,541,634.
(60) Provisional application No. 60/122,745, filed on Feb. 26, 1999.

(51) **Int. Cl.**[7] **C07D 471/04**
(52) **U.S. Cl.** **546/120**; 546/119
(58) **Field of Search** 546/120, 119

(56) **References Cited**

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WO	WO 9724369	7/1997	C07K/5/06
WO	WO 9734604	9/1997	A61K/31/445
WO	WO 9736873	10/1997	C07D/221/20
WO	WO 9858947	12/1998	C07K/5/023
WO	WO 9858948	12/1998	C07K/5/023
WO	WO 9858949	12/1998	C07K/5/06

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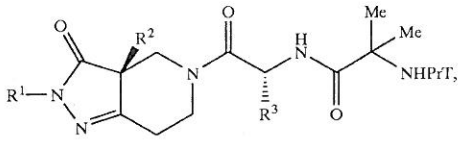
US 4,385,051, 5/1983, Oka et al. (withdrawn)
Abstract of Russian Patent 96115171 with English Translation of relevant parts.

Primary Examiner—Amelia Owens
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Gregg C. Benson; John A. Wichtowski

(57) **ABSTRACT**

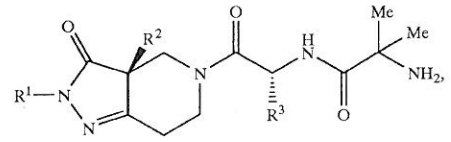
This invention relates to improved processes for preparing compounds of Formula II,

II



and compounds of Formula III,

III



wherein R^1, R^2, R^3 and Prt are defined as set forth in the specification.

53 Claims, 1 Drawing Sheet

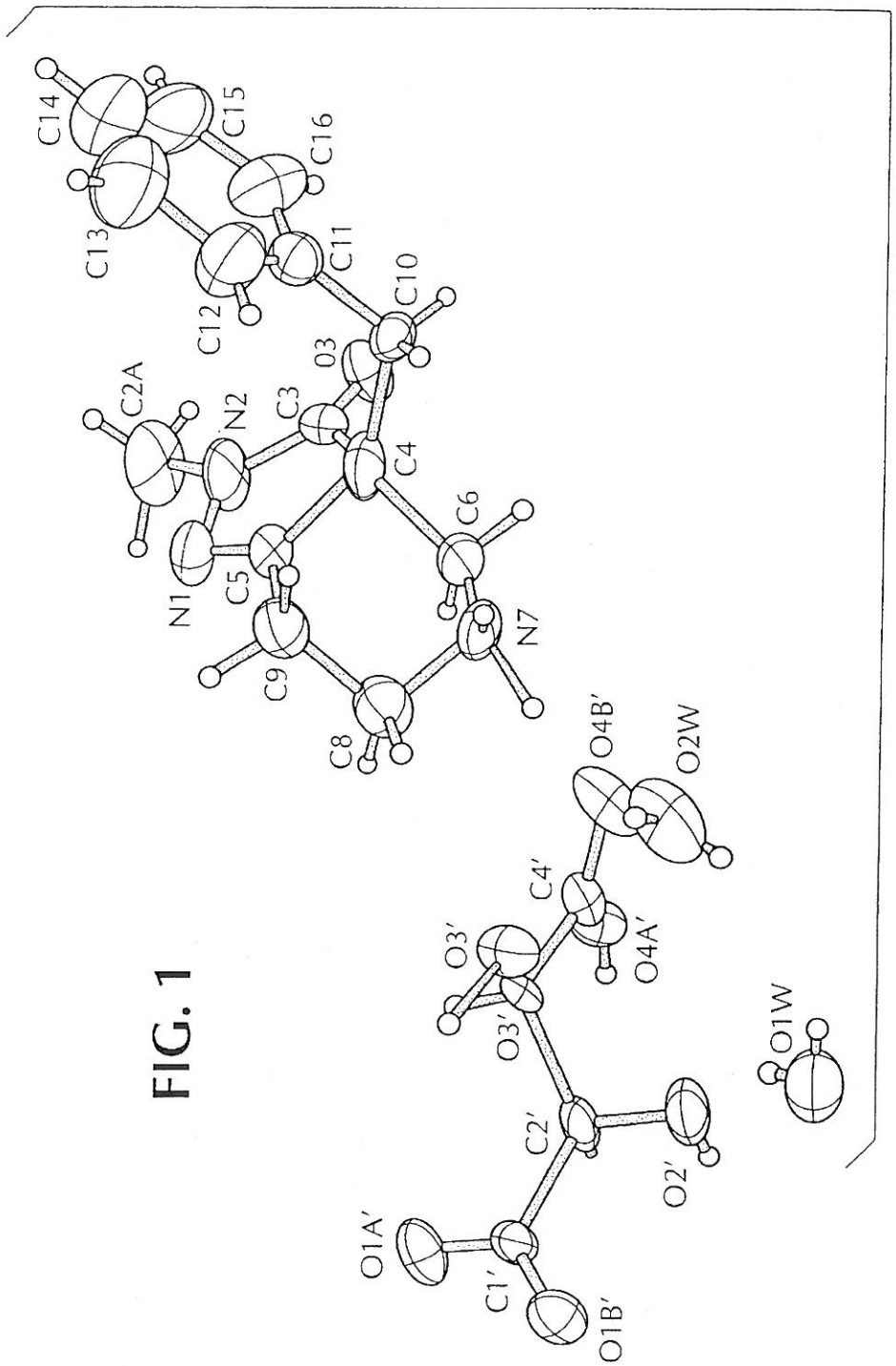

C14
C15
C16
C13
C11
C12
C10
O3
C2A
N2
C3
C4
C6
N1
C5
N7
C9
C8
O4B'
O2W
C4'
O3'
O4A'
O3'
O1W
C2'
O2'
O1A'
C1'
O1B'

FIG. 1

PROCESS FOR PREPARING GROWTH HORMONE SECRETAGOGUES

CROSS REFERENCE TO RELATED APPLICATIONS

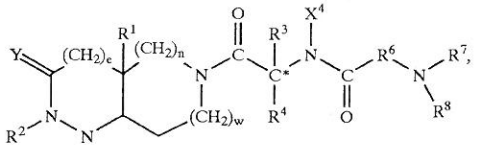
This is a divisional application of U.S. Ser. No. 09/496,075, filed Feb. 1, 2000, now U.S. Pat. No. 6,541,634 B1 which claims the benefit of U.S. Provisional Application No. 60/122,745, filed Feb. 26, 1999.

BACKGROUND OF THE INVENTION

This invention relates to an improved process for preparing compounds of Formula II comprising coupling a compound of Formula IV with a compound of Formula V. This invention also relates to an improved process for preparing compounds of Formula III by coupling a compound of Formula IV with a compound of Formula V and subsequent deprotection of the resulting Prt-protected compound of Formula II.

Commonly assigned International Patent Application Publication No. WO97/24369, hereinafter referred to as the '369 application, which is incorporated herein by reference, discloses certain growth hormone secretagogue compounds of Formula I,

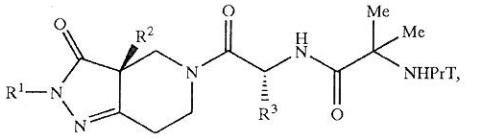
I



wherein the definitions of the variables are disclosed therein. Said compounds are disclosed in the '369 application to have utility in treating, inter alia, osteoporosis.

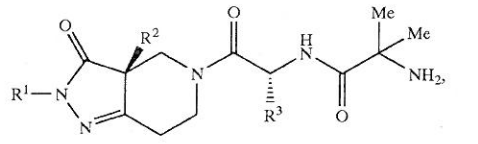
Compounds of Formula II,

II



are disclosed in the '369 application as intermediates in a process to prepare the compounds of Formula III,

III



which are within the scope of the disclosure of said international application.

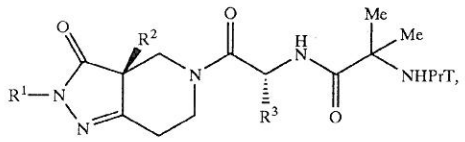
The process disclosed in the '369 application requires coupling a compound of Formula IV with a compound of Formula V. The first step in the coupling reaction is the reaction of a compound of Formula IV below with an organic amine to form the free base of the compound of Formula IV and the organic amine salt of tartaric acid. The next step in the disclosed process is a filtration step to remove the organic amine salt of tartaric acid. This was

thought to be necessary to eliminate the possibility of reaction of tartaric acid with the compound of Formula IV under the coupling conditions. Due to the racemization of the 3a position of the pyrazolo[4,3-c]pyridine which occurs at room temperature, this filtration had to be performed cryogenically, i.e., at reduced temperatures. When operating the coupling reaction on a bulk scale, cryogenic filtration presents technical problems, e.g., entrainment, slow filtration, a need to use additional equipment and extra handling. This results in reduced yields of product. In the process of this invention, the cryogenic filtration is avoided, resulting in a more streamlined process and an improved chemical and optical yield.

SUMMARY OF THE INVENTION

This invention is directed to a process, designated Process A, of preparing a compound of Formula II,

II



wherein:

R^1 is —(C_1–C_{10})alkyl optionally substituted with up to three fluoro atoms;

R^2 is phenylmethyl or 2-pyridylmethyl;

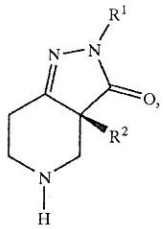
R^3 is —(C_1–C_5)alkyl-O—(C_0–C_5)alkylphenyl, where the phenyl substituent in the definition of R^3 is optionally substituted with up to three fluoro atoms; and

Prt is an amine protecting group,

comprising:

a) mixing an appropriate chiral tartrate salt having the structure of Formula IV,

IV



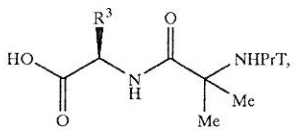
D- or L-tartaric acid

wherein R^1 and R^2 are as defined above,

and an organic amine in a reaction inert solvent at a temperature of about −68° C. to about −40° C. to form a slurry;

b) adding a compound of the Formula V,

V



wherein R^3 and Prt are as defined above, to said slurry to form a reaction mixture comprising the tartrate salt of the organic amine, the free base of a compound of Formula IV and a compound of the formula V; and

c) adding a coupling reagent to said reaction mixture to form a compound of Formula II.

A preferred process within Process A, designated Process B, is a process wherein said compound of Formula IV is suspended in said solvent prior to the addition of said organic amine.

A preferred process within Process B, designated Process C, is a process wherein said slurry is warmed to about −50° C. prior to step b.

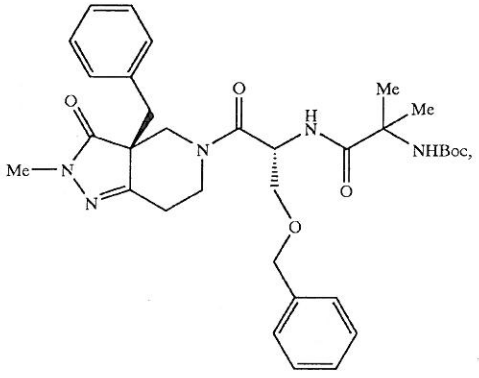
Another preferred process within Process A, designated Process D, is the process wherein: in step a, said organic amine is triethylamine; in step b, R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl and Prt is t-butyloxycarbonyl; and in step c, said coupling reagent is propane phosphonic acid anhydride.

A preferred process of Process D, designated Process E, is a process wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process of Process E is a process wherein the compound of Formula II selected from (1-(2-(1(R)-(2,4-difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester and (1-(2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester is prepared.

Another preferred process of Process E is a process wherein a compound of Formula IIA,

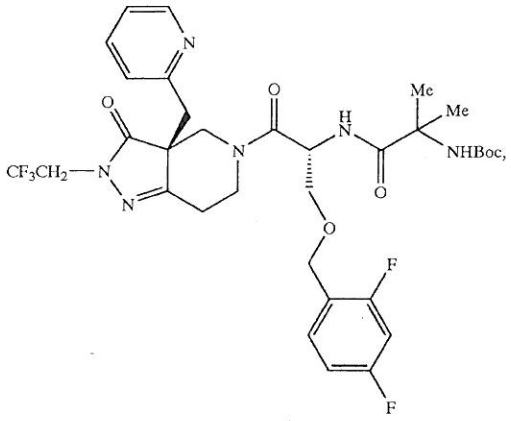
IIA



is prepared.

Another preferred process of Process E is the process wherein a compound of Formula IIB,

IIB



is prepared.

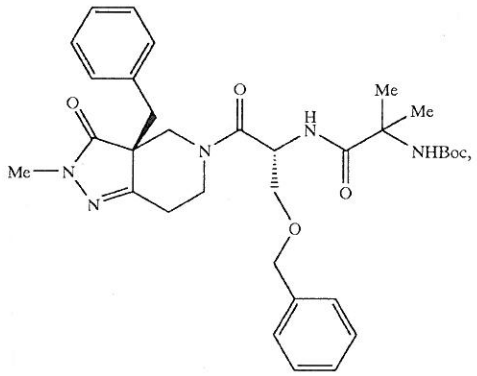
Another preferred process within Process B, designated Process F, is the process wherein: in step a, said organic amine is triethylamine; in step b, R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl and Prt is t-butyloxycarbonyl; and in step c, said coupling reagent is propane phosphonic acid anhydride.

A preferred process within Process F, designated Process G, is a process wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process within Process F is a process wherein the compound of Formula II selected from (1-(2-(1(R)-(2,4-difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a ,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester and (1-(2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester is prepared.

Another preferred process within Process F is a process wherein a compound of Formula IIA,

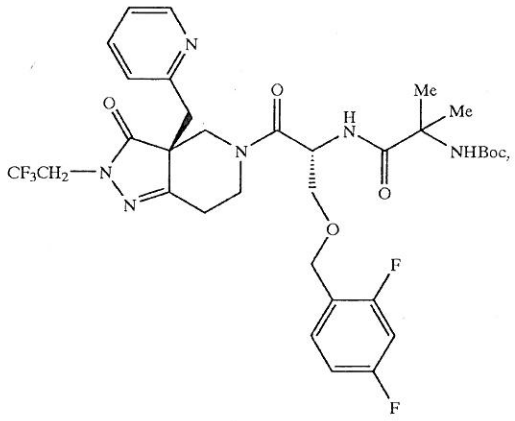
IIA



is prepared.

Another preferred process within Process F is a process wherein a compound of Formula IIB,

IIB



is prepared.

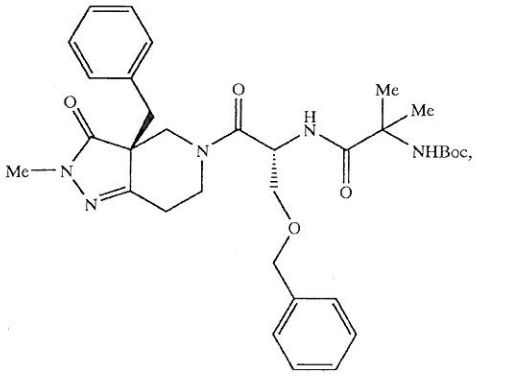
Another preferred process within Process C, designated Process H, is a process wherein: in step a, said organic amine is triethylamine; in step b, R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl and Prt is t-butyloxycarbonyl; and in step c, said coupling reagent is propane phosphonic acid anhydride.

A preferred process within Process H, designated Process I, wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process within Process I is a process wherein the compound of Formula II selected from (1-(2-(1(R)-(2,4-difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester and (1-(2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester is prepared.

Another preferred process within Process I is a process wherein a compound of Formula IIA,

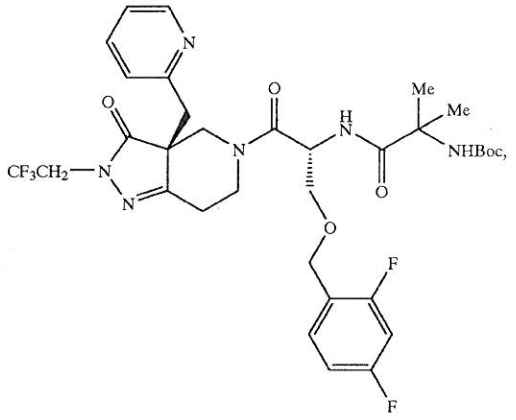
IIA



is prepared.

Another preferred process within Process I is a process wherein a compound of Formula IIB,

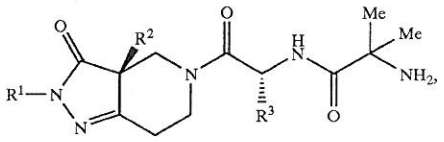
IIB



is prepared.

This invention is also directed to a process, designated Process J, for preparing a compound of Formula III,

III



wherein:

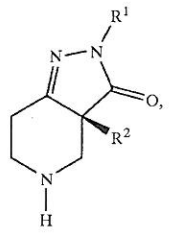
R^1 is —(C_1–C_{10})alkyl optionally substituted with up to three fluoro atoms;

R^2 is phenylmethyl or 2-pyridylmethyl; and

R^3 is —(C_1–C_5)alkyl-O—(C_0–C_5)alkylphenyl, where the phenyl substituent in the definition of R^3 is optionally substituted with up to three fluoro atoms, comprising:

a) mixing an appropriate chiral tartrate salt of the Formula IV,

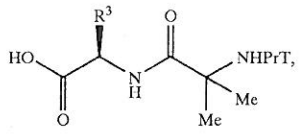
IV



D- or L-tartaric acid

wherein R^1 and R^2 are as defined above, and an organic amine in a reaction inert solvent at a temperature of about −68° C. to about −45° C. to form a slurry;

b) adding a compound of the Formula V,



V

wherein R^3 and Prt are as defined above, to said slurry to form a reaction mixture comprising the tartrate salt of the organic amine, the free base of a compound of Formula IV and a compound of the Formula V;

c) adding a coupling reagent to said reaction mixture to form a compound of Formula II; and

d) reacting said compound of Formula II with a suitable deprotecting reagent to form a compound of Formula III.

A preferred process within Process J, designated Process K, is a process wherein said compound of Formula IV is suspended in said solvent prior to the addition of said organic amine and the additional step of warming said slurry to about −50° C. to about −40° C. is effected prior to step b.

A preferred process within Process K, designated Process L, is a process wherein said Prt is Boc and said Boc is removed by reacting said compound of Formula II with an acid.

A preferred process within Process L, designated Process M, is a process wherein said acid is methanesulfonic acid.

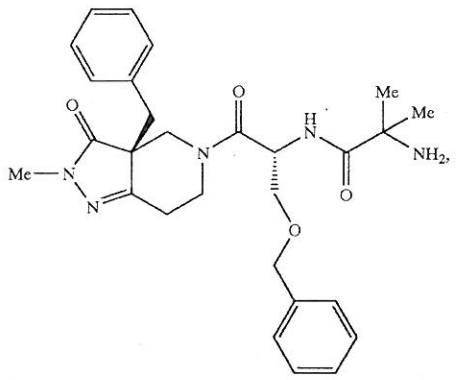
A preferred process within Process M, designated Process N, is a process wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c), said coupling reagent is propane phosphonic acid anhydride.

A preferred process within Process N, designated Process O, is a process wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process within Process O is a process wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

Another preferred process within Process O is a process wherein a compound of formula IIIA,

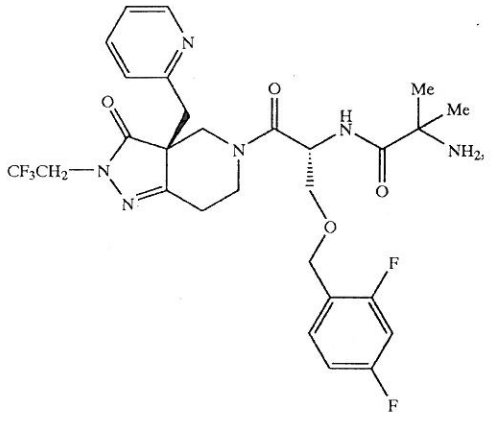
IIIA



is prepared.

Another preferred process within Process O is a process wherein a compound of formula IIIB,

IIIB



is prepared.

Another preferred process within Process L, designated Process P, is a process wherein said acid is trifluoroacetic acid.

A preferred process within Process P, designated Process R, is a process wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

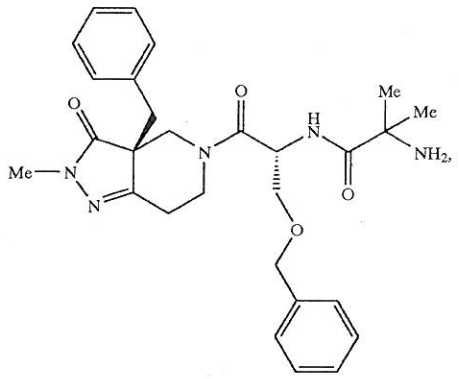
A preferred process within Process R, designated Process S, is a process wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process within Process S is a process wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-

oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

Another preferred process within Process S is a process wherein a compound of formula IIIA,

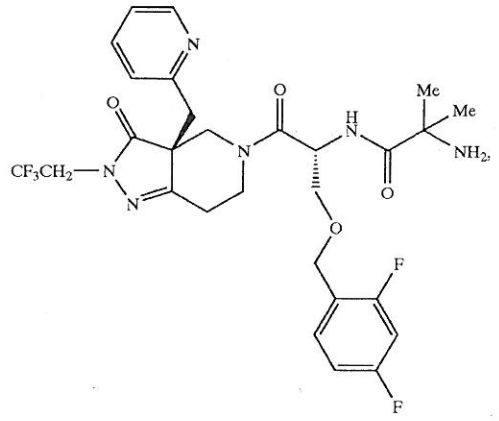
IIIA



is prepared.

Another preferred process within Process S is a process wherein a compound of formula IIIB,

IIIB



is prepared.

Another preferred process within claim K, designated Process T, is a process wherein said Prt is Boc and said Boc is removed by reacting said compound of Formula II with an acid.

A preferred process within Process T, designated Process U, is a process wherein said acid is methanesulfonic acid.

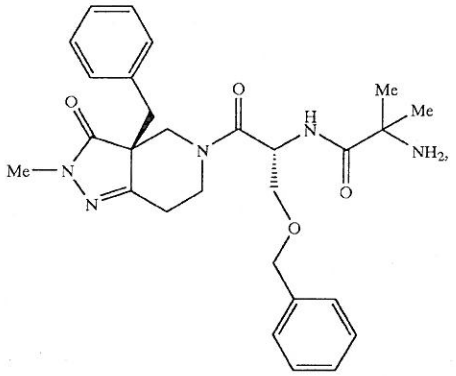
A preferred process within Process U, designated Process V, is a process wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

A preferred process within Process V, designated Process W, is a process wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process within Process W is a process wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

Another preferred process within Process W is a process wherein a compound of formula IIIA,

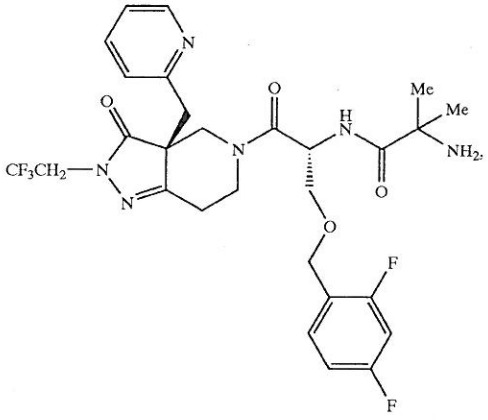
IIIA



is prepared.

Another preferred process within Process W is a process wherein a compound of formula IIIB,

IIIB



is prepared.

Another preferred process within Process T, designated Process X, is a process wherein said acid is trifluoroacetic acid.

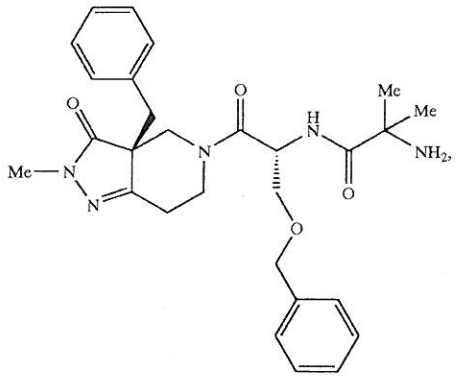
A preferred process within Process X, designated Process Y, is a process wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b), said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

A preferred process within Process Y, designated Process Z, is a process wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

A preferred process within Process Z is a process wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

Another preferred process within Process Z is a process wherein a compound of formula IIIA,

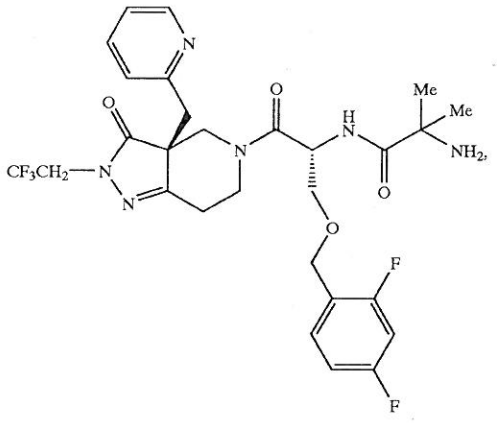
IIIA



is prepared.

Another preferred process within Process Z is a process wherein a compound of formula IIIB,

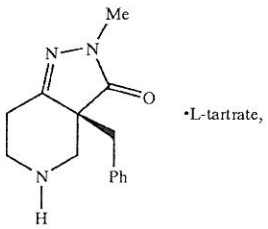
IIIB



is prepared.

This invention is also directed to a process for preparing a compound of formula XX,

XX



•L-tartrate,

comprising the following consecutive steps:

a) reacting said 4-oxo-piperidinecarboxylic acid methyl ester, hydrochloride with di-t-butyl-dicarbonate and triethylamine in isopropyl ether to form 4-oxo-1,3-piperidinedicarboxylic acid 1-(1-dimethylethyl) 3-methyl ester;

b) reacting said 4-oxo-1,3-piperidinedicarboxylic acid 1-(1-dimethylethyl) 3-methyl ester with benzyl bromide and potassium carbonate in tetrahydrofuran to form 4-oxo-(phenylmethyl)-1,3-piperidinedicarboxylic acid 1-(1-dimethylethyl) 3-methyl ester;

c) reacting said 4-oxo-(phenylmethyl)-1,3-piperidinedicarboxylic acid 1-(1-dimethylethyl) 3-methyl ester with methylhydrazine in acetic acid and methyl-t-butyl ether to form 2,3a,4,5,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid 1,1-dimethylethyl ester; and

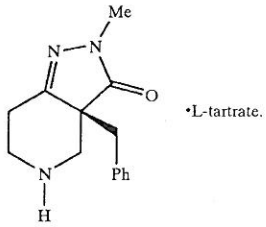
d) reacting said 2,3a,4,5,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c] pyridine-5-carboxylic acid 1,1-dimethylethyl ester with trifluoroacetic acid to form (3aR)-2,3a,4,5,6,7-hexahydro-2-methyl-3a-(phenylmethyl)-3H-pyrazolo[4,3-c]pyridin-3-one;

e) reacting said (3aR)-2,3a,4,5,6,7-hexahydro-2-methyl-3a-(phenylmethyl)-3H-pyrazolo[4,3-c] pyridin-3-one with L-tartaric acid in acetone and water to form said L-tartrate salt of formula XX.

This invention is particularly directed to a process as set forth in the immediately preceding paragraph wherein said L-tartaric acid is added without isolating said (3aR)-2,3a,4,5,6,7-hexahydro-2-methyl-3a-(phenylmethyl)-3H-pyrazolo [4,3-c]pyridin-3-one. In particular, the compound of formula XX is isolated as a dihydrate. The desired crystal form is isolated upon cooling from an appropriate mixture of solvents.

This invention is also directed to a polymorph of a dihydrate of a compound of formula XX:

XX



•L-tartrate.

This invention is particularly directed to the polymorph having the atomic coordinates and equivalent isotropic displacement coefficients as set forth in Table 1. This invention is also particularly directed to the polymorph having the X-Ray crystal structure according to FIG. 1.

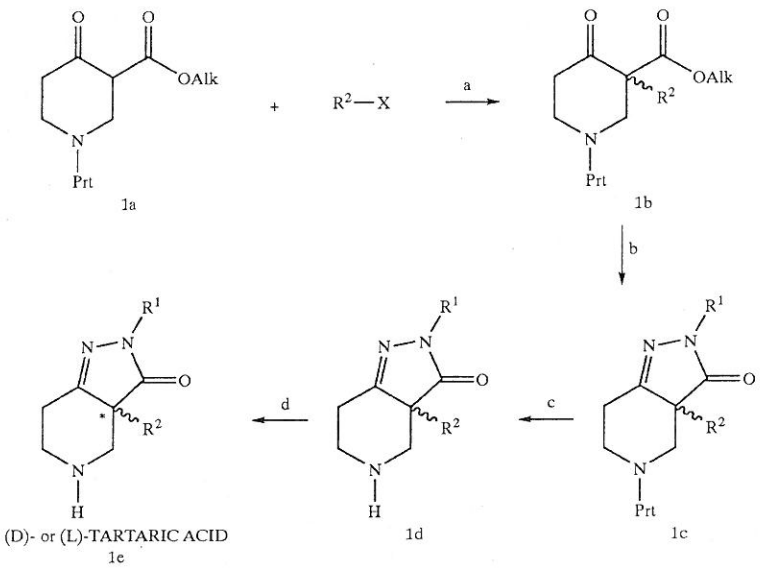
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an X-Ray crystal structure of the compound of formula XX, collected on a Siemens R3RA/v diffractometer. The crystal structure shows that the compound is a dihydrate of the L-tartrate salt of said compound.

DETAILED DESCRIPTION OF THE INVENTION

The following schemes illustrate the synthesis of the compounds of Formulas II and III. The symbol "*" indicates a stereochemical center. In the scheme "Prt" is used to indicate any suitable amine protecting group known to those skilled in the art. In the description following each scheme, the amine protecting group Prt is illustrated with the preferred amine protecting group BOC, though it will be recognized that other amine protecting groups may also be utilized.

Scheme 1



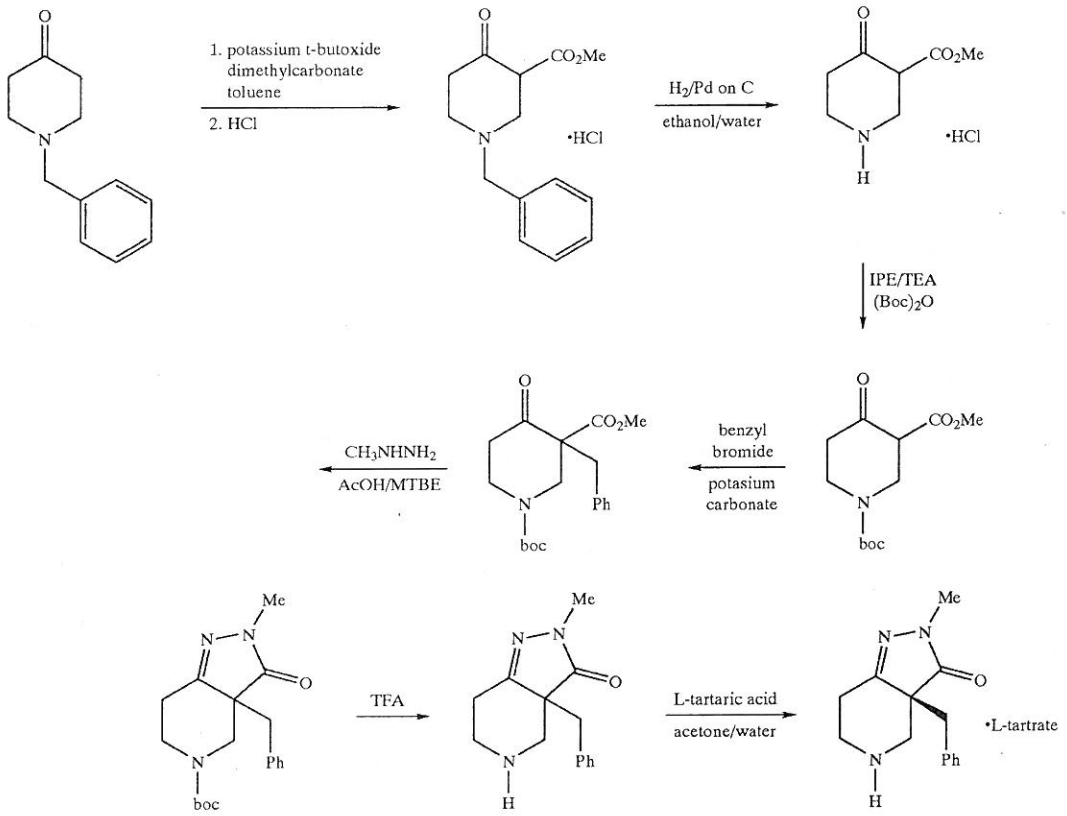
Compounds of Formula IV wherein Alk is methyl or ethyl, R^1, R^2 and Prt are as defined above, e.g., the compounds of formula 1e, are prepared as set forth in Scheme 1 or 1a. According to Scheme 1, step a, a compound of formula la is mixed with a reaction inert polar aprotic solvent such as acetone, methyl ethyl ketone, DMF (dimethylformamide) or preferably tetrahydrofuran at about 0° C. to room temperature, preferably room temperature. To the solution is added R^2—X, wherein X is a leaving group such as halo or an alkyl- or aryl-sulfonate; a base such as potassium t-butoxide or a carbonate such as Li_2CO_3, Cs_2CO_3 or preferably potassium carbonate; and optionally a phase transfer reagent such as potassium iodide or tetrabutylammonium iodide. In the case where postassium carbonate is used as base, it is preferred that a phase transfer reagent is not used. It is preferred that, where R^2 is benzyl, R^2—X is benzyl bromide and that where R^2 is 2-pyridylmethyl, R^2—X is picolyl chloride hydrochloride. After stirring at about −20° C. to about 70° C. for about 2 to 16 hours, preferably at 60° C. to about 65° C. for about 12 hours, the product is isolated from the reaction mixture according to techniques well known to those skilled in the art. This step is preferably carried out as set forth in Preparation Five, Step D, below.

According to step b, a hydrazine derivative is reacted with a compound of formula 1b. Preferably the hydrazine derivative is a 70% aqueous solution of $CF_3CH_2NHNH_2$ (trifluoroethylhydrazine) or anhydrous CH_3NHNH_2 (methylhydrazine) which is used as an aqueous solution in ethanol, water or toluene. When the 70% solution of trifluoroethylhydrazine is used, it is further preferred that the 70% aqueous solution of $CF_3CH_2NHNH_2$ is extracted with toluene. To a solution of a compound of formula 1b in an organic solvent such as ethanol, toluene or preferably methyl t-butylether (MTBE), is first added the anhydrous 2,2,2-trifluoroethyl hydrazine or methyl hydrazine, followed by acetic acid. Preferably, MTBE is used to prevent the reaction mixture from reaching a dangerously high temperature. The reaction mixture is heated at about 50° C. to about 110° C. for about 30 minutes to 24 hours, preferably about 60° C. for about 12 to about 15 hours. The reaction mixture is cooled to room temperature and neutralized with an aqueous base such as $NaHCO_3$. Where used herein, the term "room temperature" means a temperature of about 20° C.–25° C. The organic layer is separated and worked up using standard methods known in the art to yield a compound formula 1c. This step is preferably carried out as set forth in Preparation Five, Step E, below.

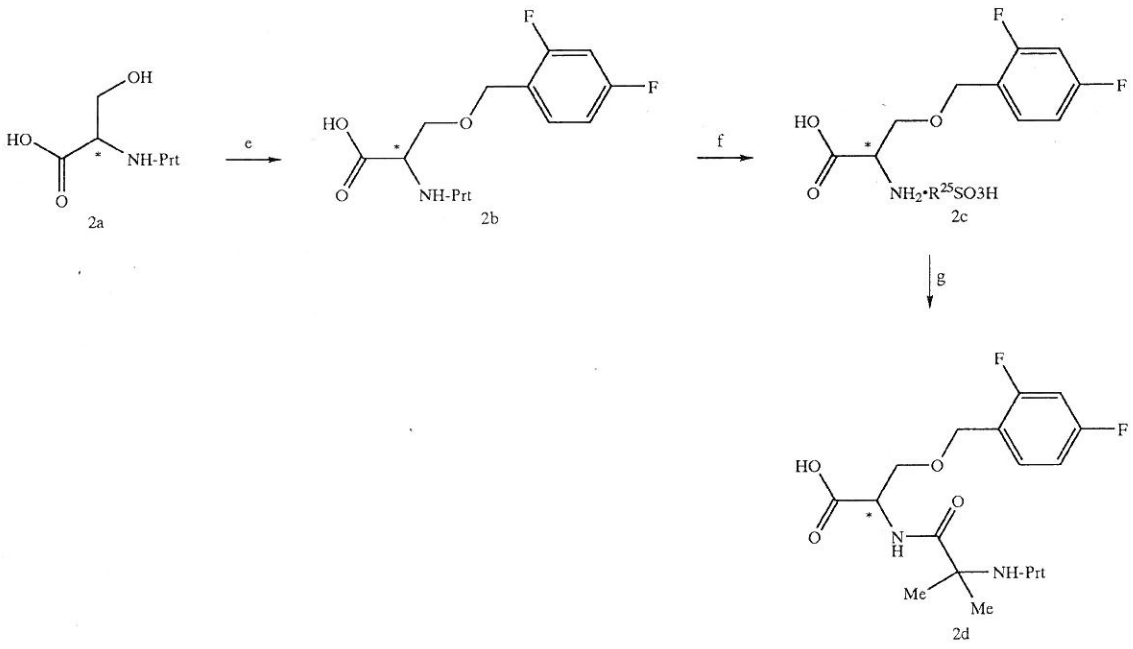
According to step c, an acid such as HCl in IPE or ethanol, trifluoroacetic acid (TFA) or an alkyl sulfonic acid such as methanesulfonic acid is added to a solution of a compound of formula 1c in a reaction inert organic solvent such as EtOH, IPE or preferably CH_2Cl_2. The mixture is stirred for about 1 to 12 hours, then cooled to about 0° C. to about room temperature, preferably to room temperature. After the reaction is complete, a base such as triethylamine or NH_4OH is added to the mixture. The mixture is allowed to warm to room temperature, is diluted with additional organic solvent and worked up using standard methods known in the art to yield a compound of formula 1d. Alternatively and preferably, the compound of formula 1d may be used without isolation in the next step. Step c of Scheme 1 is preferably carried out in combination with step d of Scheme 1 as set forth in Preparation Five, Step F, below.

According to step d, (D)- or (L)-tartaric acid, preferably (L)-tartaric acid, is added to a compound of formula 1d in acetone/water (about 8:1 to about 9:1) at about room temperature. The mixture is stirred at about room temperature to about the reflux temperature of the solvent mixture for about 1 hour to overnight, e.g., 18 hours, preferably 15 to 18 hours. Preferably the compound of formula 1e is isolated as a dihydrate crystal form. Then the solid is filtered, collected and washed with cold acetone, to yield a compound of formula 1e, which is preferably the (L)-tartrate of a single enantiomer. This step is preferably carried out as set forth in Preparation Five, Step F, without isolation of the precursor free base compound.

Scheme 1a



Scheme 2

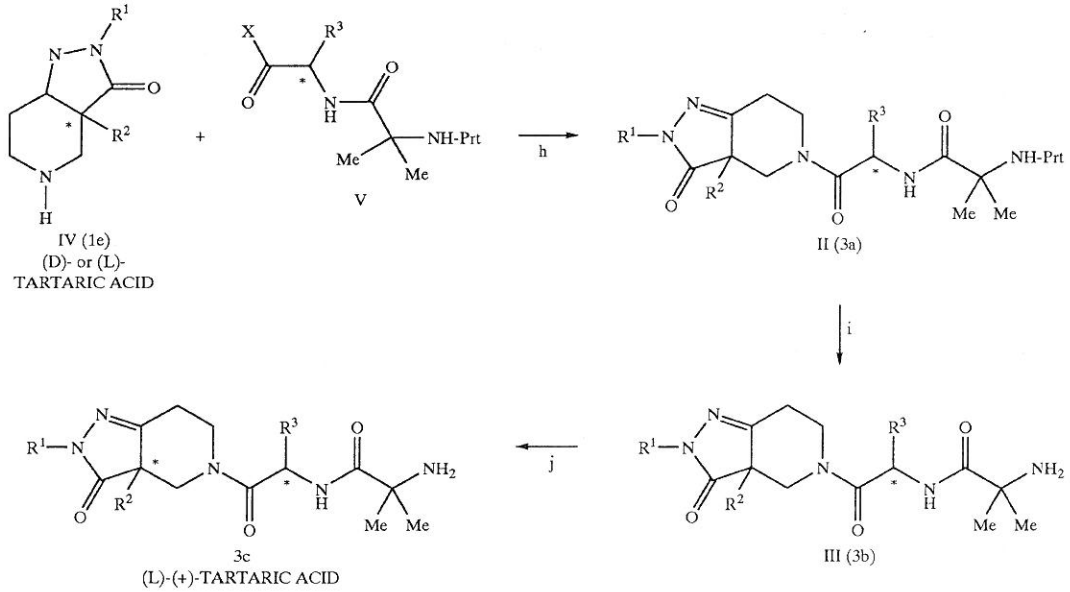


Compounds of formula V wherein R^3 is difluorobenzyloxymethyl, R^{25} is alkyl, aryl or substituted aryl and Prt is an amine protecting group, e.g., the compounds of formula 2d, are prepared as set forth in Scheme 2. According to step e, to a solution of N-BOC-serine, preferably N-BOC-(D)-serine, the compound of formula 2a, in THF/DMF (about 1:1 to about 2:1) at about 0° C. is added n-BuLi or a potassium tert-butoxide solution. The reaction mixture is stirred at about 0° C. for about 10 to about 30 minutes, preferably for 20 minutes, then 2,4-difluorobenzyl bromide is added. After warming to room temperature and stirring for about 6 to about 24 hours, the reaction mixture is concentrated in vacuo to remove the THF and an aqueous acid such as 1 N HCl is added to adjust the mixture to pH of about 3. The reaction mixture is then partitioned between water and an organic solvent such as methylene chloride (CH_2Cl_2) or IPE. The organic solution is worked up using standard methods known in the art to yield the compound of formula 2b, preferably having the R-configuration at the stereocenter, also known as the (D)-enantiomer.

According to step f, to a solution of the compound of formula 2b in an organic solvent such as THF, CH_2Cl_2, IPE or a mixture thereof, preferably CH_2Cl_2/IPE (about 1:1), is added an alkyl or aryl sulfonic acid such as methanesulfonic acid. The solid is filtered and washed with a CH_2Cl_2/IPE mixture (1:1) to afford the compound of formula 2c, preferably having the R-configuration at the stereocenter, also known as the (D)-enantiomer.

According to step g, to a solution of the compound of formula 2c in THF/water (about 4:1) is added 2-tert-butoxycarbonylamino-2-methyl-propionic acid-2,5-dioxo-pyrrolidin-1-yl ester and an alkyl amine such as triethylamine. The reaction mixture is stirred at room temperature for about 1–24 hours and quenched with an aqueous acid such as 10% aqueous citric acid solution. The mixture is partitioned with an organic solvent such as ethyl acetate and the organic layer is separated and worked-up using standard methods known in the art to yield a compound of formula 2d, preferably having the R-configuration at the stereocenter also known as the (D)-enantiomer.

The compound of Formula V wherein R^3 is benzyloxymethyl and Prt is Boc is prepared as set forth in Preparation Three, Steps A and B, below. Compounds wherein Prt is an amine protecting group other than Boc are prepared by substituting the appropriate N-protected α-methylalanine derivative for N-t-butyloxycarbonyl-α-methylalanine. Appropriate N-protected α-methylalanine derivatives, if not readily available from vendors, can be readily prepared from α-methylalanine according to methods well known to those skilled in the art.



Compounds of formulas II, III and 3c wherein R^1, R^2 and R^3 are as defined above are prepared according to Scheme 3. According to step h, a compound of formula IV (1e), preferably the (L)-tartrate salt of a single enantiomer, is slurried at about −68° C. to about −45° C., preferably at about −68° C. to about −60° C. and most preferably at about −68° C. with a reaction inert solvent, preferably ethyl acetate. An organic amine, such as diisopropylethylamine, trimethylamine or triethylamine, preferably triethylamine, is added. During the addition of the organic amine, the temperature is maintained at about −68° C. to about −45° C. and preferably at about −68° C. to about −60° C. The reaction mixture is stirred for about 30 to about 120 minutes at a temperature between about −78° C. and about −45° C. The resulting slurry contains a mixture of the free base of a compound of Formula IV and an organic amine salt of tartaric acid. To this slurry is added an organic amine such as diisopropylethylamine, trimethylamine or triethylamine, preferably triethylamine. During this addition, the internal temperature of the reaction mixture is maintained below −50° C. To this reaction mixture, which still contains an organic amine salt of tartaric acid, is added a compound of Formula V, all at once, while maintaining the temperature of the reaction mixture at about −68° C. to about −45° C. Then a coupling reagent such as propane phosphonic acid anhydride is added over a period of about 5 minutes to about 30 minutes. The temperature is allowed to warm gradually to about −25° C. to about 0° C., preferably to about −20° C. over the next hour. The reaction mixture is worked up using standard methods known in the art to yield a compound of Formula II, preferably having the absolute and relative 3a(R), 1(R) configuration.

According to step i, an acid such as HCl in EtOH, or methanesulfonic acid or trifluoroacetic acid in CH_2Cl_2 is added at about 0° C. to room temperature to a compound of Formula II in a reaction inert solvent such as CH_2Cl_2, IPE or THF. The mixture is stirred for about 40 minutes to about 4 hours at room temperature, then a saturated aqueous base such as Na_2CO_3 or $NaHCO_3$ is added until the solution is at neutral (7.0) pH. The organic layer is separated and worked up using standard methods known in the art to yield a compound of Formula II, preferably having the absolute and relative 3a(R), 1(R) configuration.

According to step j, to a solution of a compound of Formula III in an alcohol such as methanol, ethanol or isopropanol, preferably isopropanol, is added L-(+) tartaric acid. When methanol or ethanol is used, the reaction mixture is stirred for about 1 hour to about 12 hours and is then filtered and the filtrate is concentrated. In either case, the crude residue is diluted with an organic solvent such as ethyl acetate, heated and slowly allowed to cool to room temperature. The solid is filtered and dried to give the L-(+) tartaric acid salt of the compound of formula 3c, preferably having the absolute and relative 3a(R), 1(R) configuration.

The starting materials and reagents used in the processes of this invention can be purchased from common vendors or prepared according to methods well known to those skilled in the art of organic chemistry. In particular, 4-oxo-(phenylmethyl)-3-piperidinecarboxylic acid methyl ester, hydrochloride may be prepared as set forth in Preparation Five, Step A below or, alternatively, may be prepared as set forth in Hoffman, N. and Erinjeri, A., J. Heterocyclic Chem., 1965, 2, 326.

Where used herein, the term "reaction inert solvent" means a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product. Said reaction inert solvent in step a is a solvent in which the free base of the compound of Formula IV is soluble.

Where used herein, the term "organic amine" means a lower alkyl amine, such as triethylamine, trimethylamine or diisopropylethylamine; or a cyclic amine, such as piperidine, pyrrolidine or N-methylmorpholine.

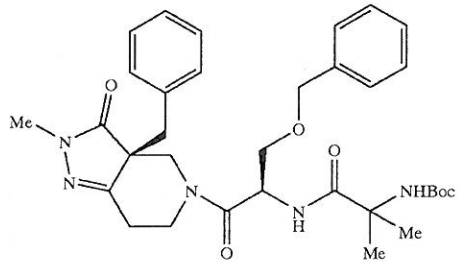
The following examples are provided for the purpose of further illustration only and are not intended to be a limitation on the disclosed invention.

Silica gel was used for column chromatography. Melting points were taken on a Buchi 510 apparatus and are uncorrected. Proton NMR spectra were recorded on a Varian XL-300, Bruker AC-300, Varian Unity 400 or Bruker AC-250 at 25° C. Those skilled in the art of organic chemistry will recognize that the NMR data obtained herein can also be obtained on other NMR insturments which are obtainable from a variety of vendors well known to those skilled in the art. Chemical shifts are expressed in parts per million down field from trimethylsilane.

General Procedure A: (Cleavage of a Boc-protecting group from a Boc-protected amine using concentrated HCl): The Boc-protected amine is dissolved in a minimum volume of ethanol and the resulting solution is cooled to about 0° C. and concentrated HCl (typically about 1 to 4 mL per mmol of Boc-protected amine) is added and the reaction mixture is warmed to room temperature and stirred for about one hour to about 2.5 hours (or the time required for complete disappearance of the starting material to a more polar product as judged by thin layer chromatography). The resulting solution or suspension is concentrated and the residue is coevaporated several times with added ethanol to afford the free amine which is used without further purification or purified as specified.

EXAMPLE 1

(1-(2-(3a(R)-Benzyl-2-methyl-3-oxo-2.3,3a.4,6.7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic Acid tert-Butyl Ester

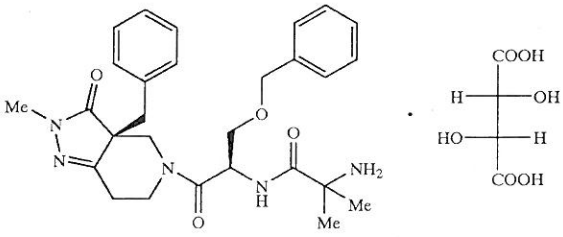


To a dry, nitrogen purged 1 liter, 4 neck, round bottom flask, equipped with a mechanical stirrer, a nitrogen capped condenser, a thermocouple, and an addition funnel was added 3a-benzyl-2-methyl-2,3,3a,4,6,7-hexahydro-pyrazolo [4,3-c]pyridin-3-one (L)-tartrate (prepared according to Preparation One, Step D, 66.09 g, 0.168 moles, 1.12 equivalents) and ethyl acetate (660 mL, 10 volumes). A slurry formed. The slurry was agitated and cooled to an internal temperature of −68° C. to −66° C. To the cooled, agitated slurry was added triethyl amine (TEA, 58 mL, 42.5 g, 0.42 moles, 2.8 equivalents) via the addition funnel. The internal temperature was maintained at −68° C. to −66° C. during addition. The reaction mixture was agitated for about 1.5 hours while the internal temperature was warmed to

about −52° C. To the reaction mixture (which was a slurry of the tartrate salt of triethylamine and the free base of 3a-benzyl-2-methyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c] pyridin-3-one (L)-tartrate) was added triethylamine (96.5 ml, 70 g, 0.69 moles, 4.6 equivalents) over 5 minutes. An internal temperature of −53° C. to −50° C. was maintained during addition. To the reaction mixture was added 3-benzyloxy-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionic acid (prepared according to Preparation Three, Step B, 57.07 g, 0.150 moles, 1.0 equivalents), all in one portion. An internal temperature −55° C. to −50° C. was maintained during addition. To the reaction mixture was added propane phosphonic acid anhydride (PPAA, 180 ml, 190 g, 2.0 equivalents) as a 50% solution of propane phosphonic acid anhydride in ethyl acetate. The PPAA was added over 15 minutes and the internal temperature rose to about −30° C. during the addition. The reaction mixture was agitated at about −30° C. for about 0.5 hours. The reaction mixture was poured into a vigorously agitated mixture of diisopropyl ether (IPE, 660 mL, 10 volumes) and water (660 mL, 10 volumes). The resulting biphasic mixture was agitated for 1 hour and then the reaction mixture was allowed to settle. The aqueous portion was decanted and the organic portion was then washed sequentially with aqueous HCl (1N, 165 mL, 2.5 volumes, 1.3 equivalents), 10% aqueous Na_2CO_3 (330 mL, 5 volumes, 2.1 equivalents), and 15% aqueous NaCl (165 mL). The washed organic portion was concentrated in vacuo to the lowest stirrable volume and to the concentrate was added IPE (300 mL, about 5 volumes). The solution was again concentrated in vacuo to the lowest stirrable volume. To the concentrate was added IPE (330 mL, about 5 volumes) and the solution was heated atmospherically to an internal temperature of about 67° C. Precipitates were observed and the slurry was cooled to an internal temperature of about 1° C. over 1 hour with agitation. The solids were filtered and dried in vacuo at about 50° C. to afford 54.85 g of the title compound (60.4% yield).

EXAMPLE TWO

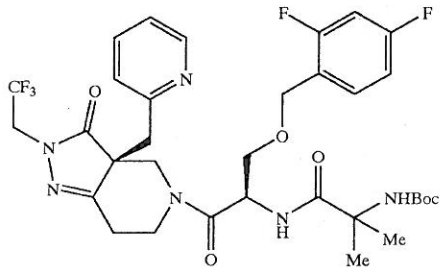
2-Amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide (L-Tartrate Salt)



To a 5L, 4 neck, round bottom flask equipped with a mechanical agitator, thermocouple, a condenser and an addition funnel, was added consecutively 3a(R)-benzyl-2-methyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one (L)-tartrate (prepared according to Preparation One, Step D, 60.57 g, 0.10 moles, 1.0 equivalent) and methylene chloride (400 ml, 6.7 volumes). The mixture was agitated to afford a clear solution and the solution was then cooled to an internal temperature of −10° C. to −5° C. To the cooled, agitated solution was added trifluoroacetic acid (TFA, 180 ml, 3.0 volumes/23.6 equivalents/2.33 moles) at such a rate that the internal temperature did not exceed −5° C. The addition was complete in about 10 minutes. The reaction mixture was then slowly warmed to 8° C. over 1 hour. While maintaining an internal temperature of 10° C.–20° C., the reaction mixture was brought to pH greater than 8 by slow addition of Na_2CO_3 (1.0 N, 1200 ml, 12 equivalents/12 moles). The reaction mixture was allowed to settle and the organic portion was decanted. The aqueous fraction was extracted with methylene chloride (2×100 ml portions, 1.65 volumes each). The combined organic fractions were washed with water (100 mL). The washed organic fraction was concentrated to the lowest stirrable volume by atmospheric distillation and to the concentrate was added ethyl acetate (2000 ml, 33 volumes). To the ethyl acetate solution was added a solution L-tartaric acid (15.05 g, 0.10 moles/1 equivalent) in methanol (60 ml, 1 volume). The reaction mixture was heated and the methanol distilled off. The distillation was continued until the internal and head temperature were 77° C.–78° C. and then the reaction mixture was refluxed for 1–2 hours. The reaction was then cooled to about 1 5° C. over several hours. The solids were filtered, washed with ethyl acetate (200 ml) and dried overnight in vacuo at about 50° C. to afford 60.79 g of the title compound (92.7% yield).

EXAMPLE THREE

(1-(2-(1(R)-(2,4-Difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic Acid tert-Butyl Ester

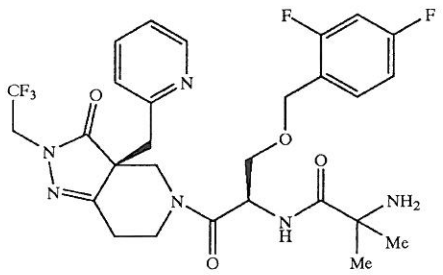


To a dry, nitrogen purged 0.5 liter, 4 neck, round bottom flask, equipped with a mechanical stirrer, a nitrogen capped condenser, a thermocouple, and an addition funnel were added sequentially 3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c] pyridin-3-one (L)-tartrate (prepared according to Preparation Two, Step D, 10.35 g, 0.0224 moles, 1.12 equivalents) and ethyl acetate (110 mL, 10 volumes). A slurry formed. The slurry was agitated and cooled to an internal temperature of −68° C. to −60° C. To the cooled, agitated slurry was added triethylamine (TEA, 7.75 ml, 5.66 g, 0.056 moles, 2.8 equivalents) via the addition funnel. The internal temperature was maintained at −68° C. to −60° C. during addition. The reaction mixture was agitated for about 1.5 hours while the internal temperature was warmed to about −62° C. to −52° C. To the reaction mixture (which was a slurry of the tartrate salt of triethylamine and the free base of 3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one (L)-tartrate) was added triethylamine (12.7 ml, 9.30 g, 0.092 moles, 4.6 equivalents) over 5 minutes. An internal temperature of −62° C. to −50° C. was maintained during addition. To the reaction mixture

was added 2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-3-(2,4-difluoro-benzyloxy)-propionic acid (prepared according to Preparation Four, Step C, 8.34 g, 0.020 moles, 1.0 equivalents), all in one portion. An internal temperature of −60° C. to −58° C. was maintained during addition. Propane phosphonic acid anhydride (PPM, 24 mL, 25.5 g, 2.0 equivalents) as a 50% solution of propane phosphonic acid anhydride in ethyl acetate was diluted with ethyl acetate (24 mL, 2.2 volumes) and cooled to about −45° C. The PPM solution was then added to the reaction mixture. The PPM was added over 15 minutes and the internal temperature rose gradually to about −19° C. over about 1 hour. The reaction mixture was poured into a vigorously agitated mixture of diisopropyl ether (IPE, 100 mL, 9.1 volumes) and water (100 mL, 9.1 volumes). The resulting biphasic mixture was agitated for 5 minutes and then the reaction mixture was allowed to settle. The aqueous portion was decanted and the organic portion was then washed sequentially with aqueous HCl (0.5N, 50 mL, 4.5 volumes, 1.3 equivalents), saturated aqueous $NaHCO_3$ (50 mL, 4.5 volumes, ~2.5 equivalents), and 15% aqueous NaCl (50 mL). The washed organic portion was concentrated in vacuo to afford an oil. The oil was agitated with hexanes (50 mL, about 2.5 volumes) to afford a glassy solid, 13.75 g (96.8% crude yield). The solids were dissolved in chloroform and concentrated in vacuo to afford an oil. This procedure was repeated with hexanes. Finally, the resultant oil was agitated with hexanes for 16 hours. The resultant solids were filtered to afford 10.45 g of the title compound (73.6% yield).

EXAMPLE FOUR

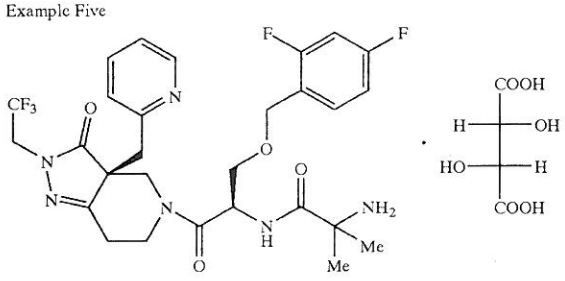
2-Amino-N-(1(R)-(2.4-difluoro-benzyloxmethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide



(1-(2-(1(R)-(2,4-Difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester (prepared according to Example Three, 17.5 g, 25.3 mmol) was deprotected according to the method described in General Procedure A to afford a colorless solid. The product was triturated with diethyl ether to afford the title compound. (13.6 g, 90%):+Apcl MS $(M+H)^+$591.

EXAMPLE FIVE

Example Five



2-Amino-N-{1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide L-(+) Tartrate

To a solution of 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide (prepared according to Example Four, 370 g, 0.6 mol) in methanol (4,070 mL) in a 12 L round bottom flask equipped with a mechanical stirrer was added L-(+) tartaric acid (90 g, 0.6 mol). The reaction mixture was stirred for about 90 min. at about 22° C., filtered and concentrated. The crude residue was diluted with ethyl acetate (4,560 mL), heated at about 70° C. and slowly allowed to cool to room temperature over about 17 hours. The solid was filtered and dried to give white crystals, mp 188–189° C. (348.46 g, yield 76%). ^1H NMR (MeOH, d4) δ: 8.28 (d, 1H), 7.59 (t, 1H), 7.41–7.39 (m, 1H), 7.18–7.13 (m, 1H), 6.92 (t, 1H), 5.2 (t, 1H), 4.56 (bs, 3H), 4.36 (s, 2H), 4.31–4.25 (m, 1H), 4.13–4.06 (m, 1H), 3.78 (d, 2H), 3.21 (t, 1H), 3.18–2.96 (m, 2H), 2.65–2.55 (m, 2H), 1.57 (d, 6H). MS: MH+ 611. $[a]^{589}$+ 22.03 (c=11.9, MeOH).

EXAMPLE SIX

Single Crystal X-Ray Analysis. A representative crystal was surveyed and a 1 Å data set (maximum θ/λ=0.5) was collected on a Siemens R^3RA/V diffractometer. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[1] All crystallographic calculations were facilitated by the SHELXTL[2] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table 1 below.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogens on the nitrogen and oxygen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 4.95%. A final difference Fourier revealed no missing or misplaced electron density.

The refined structure was plotted using the SHELXTL plotting package (FIG. 1). The absolute configuration was assigned on the known configuration of L-tartaric acid. Coordinates, anisotropic temperature factors, distances and

angles are available as supplementary material, see Tables II through VI.

TABLE I

Single Crystal X-Ray Crystallographic Analysis

A. Crystal Parameters:	
formula	$C_{14}H_{18}N_3O^+$ $C_4H_5O_6^-$ · $2H_2O$ (429.4)
crystallization medium	acetone and water (4:1)
crystal size, mm	0.05 × 0.12 × 0.32
cell dimensions	a = 8.235 (3) Å b = 7.032 (2) Å c = 18.106 (6) Å α = 90.0° β = 99.41 (2)° γ = 90.0° V = 1034.4 (6) Å^3
space group	$P2_1$
molecules/unit cell	2
density calcd, g/cm^3	1.379
linear absorption factor, mm^{-1}	0.946
B. Refinement Parameters:	
number of reflections	1174.39
nonzero reflections (I > 3.0σ)	1025
R-index[a]	4.95%
GOF[b]	1
secondary extinction factor[c], $_\chi$	52 (8) × 10^{-4}

a R-index = Σ ‖ Fo | − | Fc |/Σ | Fo |

b GOF = [Σw(Fo^2 − Fc^2)^2/(m − s)]^{½} where w = [σ^2 (F) + | g | F^2]$^{-1}$ and g = 0.0005

c F* = F[1 + 0.002$_\chi$F^2/sin(2θ)]$^{-¼}$

TABLE II

Atomic coordinates (×10^4) and equivalent isotropic displacement coefficients (Å^2 × 10^3)

	x	y	z	U(eq)
C(1')	7050 (7)	12045 (7)	6424 (4)	31(1)
O(1A')	5715 (5)	12748 (6)	6097 (3)	41(1)
O(1B')	8234 (5)	12946 (6)	6748 (3)	41(1)
C(2')	7120 (6)	9881 (7)	6388 (4)	29(1)
O(2')	8733 (5)	9232 (6)	6715 (3)	37(1)
C(3')	6707 (7)	9167 (7)	5599 (4)	32(1)
O(3')	7899 (5)	9726 (6)	5160 (3)	47(1)
C(4')	6647 (7)	6999 (7)	5583 (4)	32(1)
O(4A')	5644 (5)	6263 (6)	5971 (3)	39(1)
O(4B')	7465 (5)	6110 (7)	5213 (3)	59(1)
N(1)	5011 (6)	8379	1995 (3)	43(1)
N(2)	4317 (6)	6558 (7)	1896 (3)	40(1)
C(2A)	2623 (6)	6380 (8)	1541 (4)	55(1)
C(3)	5357 (7)	5149 (8)	2171 (4)	36(1)
O(3)	5039 (5)	3491 (6)	2188 (3)	46(1)
C(4)	6998 (6)	6172 (8)	2450 (3)	28(1)
C(5)	6515 (6)	8177 (8)	2299 (4)	33(1)
C(6)	7511 (6)	5878 (8)	3290 (4)	39(1)
N(7)	8723 (6)	7355 (7)	3591 (3)	40(1)
C(8)	8153 (7)	9366 (8)	3440 (4)	49(1)
C(9)	7643 (7)	9700 (8)	2603 (4)	46(1)
C(10)	8290 (6)	5440 (8)	1989 (4)	37(1)
C(11)	7862 (7)	5776 (8)	11667 (4)	43(1)
C(12)	8463 (7)	7317 (8)	853 (4)	69(1)
C(13)	8108 (8)	7675 (9)	76 (5)	97(1)
C(14)	7080 (*)	6405 (9)	−336 (5)	96(1)
C(15)	6443 (8)	4882 (8)	−59 (5)	81(1)
C(16)	6872 (7)	4533 (8)	705 (4)	75(1)
O(1W)	8100 (5)	6278 (7)	7609 (3)	54(1)
O(2W)	10828 (5)	8138 (7)	5099 (3)	62(1)

*Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

*Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

TABLE III

Bond Lengths (Å)

C(1')–O(1A')	1.262(7)	C(1')–O(1B')	1.229(7)
(C1')–C(2')	1.525(7)	C(2')–O(2')	1.4347(6)
C(2')–C(3')	1.500(9)	C(3')–O(3')	1.416(8)
C(3')–C(4')	1.526(7)	C(4')–O(4A')	1.277(8)
C(4')–O(4B')	1.201(8)	N(1)–N(2)	1.402(5)
N(1)–C(5)	1.278(7)	N(2)–C(2A)	1.443(7)
N(2)–C(3)	1.350(7)	C(3)–O(3)	1.196(7)
C(3)–C(4)	1.541(7)	C(4)–C(5)	1.478(7)
C(4)–C(6)	1.526(9)	C(4)–C(10)	1.544(9)
C(5)–C(9)	1.465(7)	C(6)–N(7)	1.481(7)
N(7)–C(8)	1.501(7)	C(8)–C(9)	1.524(10)
C(10)–C(11)	1.492(9)	C(11)–C(12)	1.355(9)
C(11)–C(16)	1.380(8)	C(12)–C(13)	1.411(12)
C(13)–C(14)	1.365(9)	C(14)–C(15)	1.327(10)
C(15)–C(16)	1.393(11)		

TABLE IV

Bond Angles (°)

O(1A')–C(1')–O(1B')	125.8(5)	O(1A')–C(1')–C(2')	114.1(5)
O(1B')–C(1')–C(2')	120.2(5)	C(1')–C(2')–O(2')	109.8(4)
C(1')–C(2')–C(3')	111.7(5)	O(2')–C(2')–C(3')	109.7(5)
C(2')–C(3')–O(3')	111.9(4)	C(2')–C(3')–C(4')	110.7(5)
O(3')–C(3')–C(4')	106.9(5)	C(3')–C(4')–O(4A')	114.6(5)
C(3')–C(4')–O(4B')	120.7(6)	O(4A')–C(4')–O(4B')	124.6(5)
N(2)–N(1)–C(5)	107.4(3)	N(1)–N(2)–C(2A)	118.7(4)
N(1)–N(2)–C(3)	113.8(4)	C(2A)–N(2)–C(3)	127.5(5)
N(2)–C(3)–O(3)	126.6(5)	N(2)–C(3)–C(4)	104.3(4)
O(3)–C(3)–C(4)	129.0(5)	C(3)–C(4)–C(5)	100.9(4)
C(3)–C(4)–C(6)	110.4(5)	C(5)–C(4)–C(6)	109.6(5)
C(3)–C(4)–C(10)	108.2(5)	C(5)–C(4)–C(10)	114.0(5)
C(6)–C(4)–C(10)	113.0(4)	N(1)–C(5)–C(4)	113.4(4)
N(1)–C(5)–C(9)	126.2(4)	C(4)–C(5)–C(9)	119.5(4)
C(4)–C(6)–N(7)	109.4(5)	C(6)–N(7)–C(8)	115.0(4)
N(7)–C(8)–C(9)	110.7(5)	C(5)–C(9)–C(8)	108.4(5)
C(4)–C(10)–C(11)	114.5(4)	C(10)–C(11)–C(12)	120.2(5)
C(10)–C(11)–C(16)	121.6(6)	C(12)–C(11)–C(16)	118.3(7)
C(11)–C(12)–C(13)	122.0(6)	C(12)–C(13)–C(14)	115.9(7)
C(13)–C(14)–C(15)	124.7(8)	C(14)–C(15)–C(16)	117.8(6)
C(11)–C(16)–C(15)	121.2(6)		

TABLE V

Anisotropic displacement coefficients (Å^2 × 10^3)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1')	32 (1)	26 (1)	34(1)	2 (1)	5 (1)	−8 (1)
O(1A')	35 (1)	19 (1)	67(1)	−4 (1)	2 (1)	2 (1)
O(1B')	35 (1)	26 (1)	60(1)	−4 (1)	−2 (1)	−13 (1)
C(2')	32 (1)	17 (1)	36(1)	1 (1)	−1 (1)	1 (1)
O(2')	32 (1)	33 (1)	43(1)	4 (1)	−1 (1)	0 (1)
C(3')	41 (1)	18 (1)	37(1)	6 (1)	6 (1)	−6 (1)
O(3')	71 (1)	33 (1)	41(1)	−2 (1)	23 (1)	1 (1)
C(4')	28 (1)	27 (1)	39(1)	2 (1)	3 (1)	2 (1)
O(4A')	41 (1)	32 (1)	45(1)	−7 (1)	10 (1)	−9 (1)
O(4B')	56 (1)	35 (1)	92(1)	7 (1)	32 (1)	−2 (1)
N(1)	39 (1)	48 (1)	37(1)	4 (1)	−6 (1)	7 (1)
N(2)	30 (1)	39 (1)	47(1)	2 (1)	−2 (1)	−4 (1)
C(2A)	27 (1)	66 (1)	68(1)	−3 (1)	−2 (1)	−1 (1)
C(3)	39 (1)	40 (1)	30(1)	8 (1)	10 (1)	−7 (1)
O(3)	45 (1)	27 (1)	65(1)	−3 (1)	5 (1)	1 (1)
C(4)	23 (1)	34 (1)	26(1)	0 (1)	2 (1)	3 (1)
C(5)	31 (1)	32 (1)	36(1)	−1 (1)	6 (1)	0 (1)
C(6)	38 (1)	38 (1)	38(1)	4 (1)	1 (1)	−4 (1)
N(7)	39 (1)	42 (1)	34(1)	1 (1)	−6 (1)	−1 (1)
C(8)	44 (1)	46 (1)	54(1)	−1 (1)	1 (1)	−9 (1)
C(9)	41 (1)	42 (1)	52(1)	6 (1)	2 (1)	0 (1)
C(10)	37 (1)	46 (1)	29(1)	6 (1)	9 (1)	4 (1)

TABLE V-continued

	Anisotropic displacement coefficients (Å² × 10³)					
	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(11)	39 (1)	55 (1)	37(1)	10 (1)	7 (1)	-2 (1)
C(12)	72 (1)	85 (1)	49(1)	4 (1)	2 (1)	1 (1)
C(13)	103 (1)	108 (1)	82(1)	2 (1)	16 (1)	27 (1)
C(14)	103 (1)	108 (1)	73(1)	13 (1)	4 (1)	6 (1)
C(15)	81 (1)	93 (1)	63(1)	-4 (1)	-6 (1)	-17 (1)
C(16)	80 (1)	88 (1)	58(1)	-4 (1)	13 (1)	-12 (1)
O(1W)	56 (1)	45 (1)	60(1)	-7 (1)	7 (1)	-2 (1)
O(2W)	58 (1)	48 (1)	91(1)	3 (1)	42 (1)	7 (1)

The anisotropic displacement exponent takes the form:

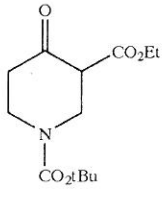
$$-2\pi^2(h^2a^{*2}U_{11}+\ldots+2hka^*b^*U_{12})$$

TABLE VI

	H-Atom coordinates (×10⁴) and isotropic displacement coefficients (Å² × 10³)			
	x	y	z	U
H(2')	6314	9385	6665	80
H(2A')	8195 (10)	8867 (10)	7105 (9)	50
H(3')	5656	9704	5398	80
H(3A')	8259 (10)	11720 (10)	5037 (9)	50
H(4A')	5234 (10)	6488 (10)	6270 (9)	50
H(2A)	2319	5061	1512	80
H(2B)	2495	6907	1046	80
H(2C)	1928	7053	1829	80
H(6A)	7999	4642	3381	80
H(6B)	6562	5972	3533	80
H(7A)	9771 (10)	7980 (10)	3431 (9)	50
H(7B)	9183 (10)	7721 (10)	4160 (9)	50
H(8A)	7229	9605	3689	80
H(8B)	9033	10220	3630	80
H(9A)	8599	9685	2362	80
H(9B)	7101	10908	2520	80
H(10A)	8417	4095	2071	80
H(10B)	9315	6067	2166	80
H(12)	9152	8192	1169	80
H(13)	8559	8747	-149	80
H(14)	6799	6628	-864	80
H(15)	5710	4049	-375	80
H(16)	6471	3406	915	80
H(1WA)	8471 (10)	5946 (10)	7323 (9)	52(1)
H(1WB)	6863 (10)	5969 (10)	7529 (9)	50
H(2WA)	11347 (10)	8095 (10)	5456 (9)	50
H(2WB)	11515 (10)	9176 (10)	4829 (9)	50

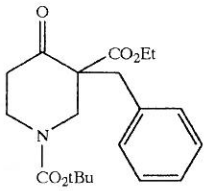
Preparation One

Step A. 4-oxo-Piperidine-1,3-dicarboxylic Acid 1-tert-Butyl Ester 3-Methyl Ester.



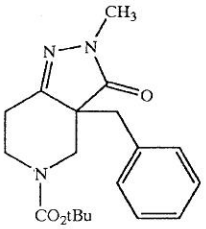
To a mixture of 7.00 g (36.2 mmol) of 4-oxo-piperidine-3-carboxylic acid methyl ester and 8.82 g (72.3 mmol) of 4,4-dimethylaminopyridine in 200 mL of methylene chloride at about 0° C. was added a solution of 7.88 g (36.2 mmol) of di-tert-butyldicarbonate in 150 mL of methylene chloride over about 30 min. The mixture was warmed to room temperature and then stirred for about 17 h. The mixture was concentrated and the residue was diluted with chloroform and washed three times each with 10% aqueous HCl, saturated aqueous sodium bicarbonate solution and brine, dried over $MgSO_4$ and concentrated to give 9.18 g of a clear yellow oil.

Step B. 3-(R,S)-Benzyl-4-oxo-piperidine-1,3-dicarboxylic Acid 1-tert-Butyl Ester 3-Methyl Ester.



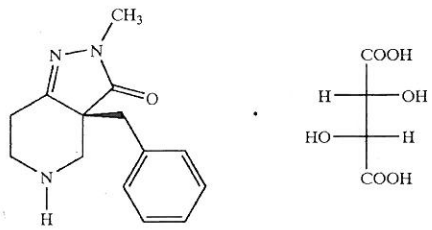
To a solution of the compound prepared according to Step A (5.00 g, 19.4 mmol) in 10 mL of DMF was added 745 mg (7.4 mmol) of sodium hydride (60% oil dispersion) and the mixture was stirred at room temperature for about 15 min. A solution of 3.32 g (19.4 mmol) benzylbromide in 15 mL of DMF was added to the stirring solution by cannula and the mixture was stirred for about 42 h at room temperature. The mixture was diluted with ethyl acetate and washed once with water and four times with brine, dried over $MgSO_4$, and concentrated to give 6.0 g of the title compound of Step B as a yellow oil. MS (Cl, NH_3) 348 (MH^+).

Step C. 3a-(R,S)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]-pyridine-5-carboxylic Acid tert-Butyl Ester.



A mixture of the compound prepared according to Step B (4.00 g, 11.5 mmol) and 530 mg (11.5 mmol) of methylhydrazine in 100 mL of ethanol was heated at reflux for about 8 h. The mixture was concentrated and the residue was dissolved in 100 mL toluene and heated at reflux for about 17 h. The mixture was concentrated and the residue was purified by silica gel chromatography using an elution gradient of (15:85 v/v ethyl acetate:hexane) to (75:25 v/v ethyl acetate:hexane) to give 2.6 g of the title compound of Step C as a clear colorless oil. MS (Cl, NH_3) 344 (MH^+).

Step D. 3a(R)-Benzyl-2-methyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one (L)-Tartrate.

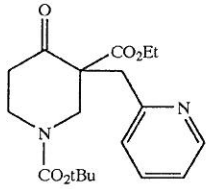


To a 2 liter, round bottom flask, equipped with a mechanical stirrer, addition funnel, and a thermocouple was added, sequentially, 3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-

hexahydro-pyrazolo[4,3-c]-pyridine-5-carboxylic acid tert-butyl ester (prepared according to Step C, 51.5 g, 0.15 moles, 1.0 equivalents) and methylene chloride (515 ml, 10 volumes). The mixture was agitated to form a solution which was then cooled to an internal temperature of 0° C.–5° C. To the cooled mixture was added trifluoroacetic acid (TFA, 130 ml, 192 g, 1.68 moles, 11.2 eq., 2.5 volumes). The TFA was added via the addition funnel over 15 minutes while maintaining an internal temperature of 0° C.–5° C. The reaction mixture was warmed to about 20° C. over 3 hours and then the reaction mixture was cooled to 10° C.–15° C. To the cooled reaction mixture was added sodium carbonate (92 g, 0.868 moles) in water (920 mL) over 20 minutes. The pH was 7.5. The reaction mixture was transferred to a 2 liter separatory funnel and allowed to settle. The organic portion was decanted and the aqueous portion was extracted with methylene chloride (130 ml, 2.5 volumes). The combined organic portions were transferred back to the 2 liter reactor and to it was added L-tartaric acid (24.77 g, 0.165 moles, 1.1 equivalents) dissolved in acetone (354 ml, about 7 volumes) and water (44 mL, about 1 volume). The reaction mixture was agitated and heated at about 38° C. overnight. The resultant slurry was cooled to 0° C.–5° C., granulated for 1 hour, then filtered. The solids were washed with 100 ml of cold acetone and then dried in vacuo at 40° C.–50° C. for 16 hours to afford 51.86 g (87.9% yield) of the title compound of Step D.

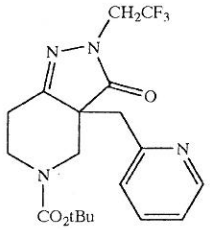
Preparation Two

Step A 4-oxo-3-Pyridin-2-yl-methyl-piperidine-1,3-dicarboxylic Acid 1-tert-Butyl Ester 3-Ethyl Ester.



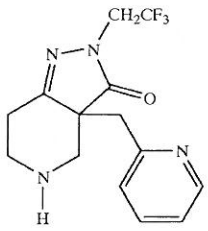
To a solution of 4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (prepared according to the method of Preparation One, Step A, 10.34 g, 38.2 mmol) in DMF (40 mL) at about 0° C. was added picolyl chloride hydrochloride (5.7 g, 34.7 mmol), potassium carbonate (14.4 g, 104.1 mmol) and potassium iodide (5.76 g, 34.7 mmol). After stirring at about 0° C. for about 2 hours, the ice bath was removed and DABCO (973 mg, 8.68 mmol) was added. The reaction mixture was stirred for about 30 min. and poured into a mixture of water and IPE. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was crystallized from hexanes to give a white solid (8.19 g, yield 65%). ^{1}H-NMR ($CDCl_3$) δ 1.17 (t, 3H), 1.48 (s, 9H), 1.55 (s, 2H), 2.61 (m, 1H), 2.71 (m, 1H), 3.31–3.50 (m, 3H), 4.11 (d, 2H), 4.49 (d, 1H), 7.06 (br, s, 1H), 7.17 (d, 1H), 7.54 (m, 1H), 8.40 (s, 1H).

Step B. 3-oxo-3a-Pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic Acid tert-Butyl Ester.



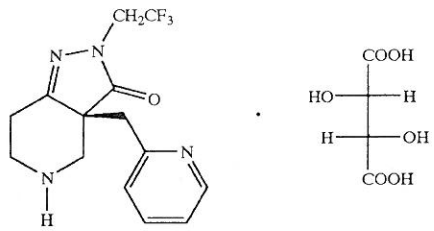
A 70% aqueous solution of $CF_3CH_2NHNH_2$ (325 mL, 1.986 mol) was extracted with toluene (3×1200 mL). To a solution of the compound prepared according to step A (600 g, 1.655 mol) in toluene (900 mL) was first added the combined toluene extracts containing the anhydrous 2,2,2-trifluoroethyl hydrazine, followed by acetic acid (121.4 g, 1.986 mol). The reaction mixture was heated at about 70° C. for about 2 hours, then another toluene extraction of 70% aqueous 2,2,2-trifluoroethyl hydrazine (50 g) was added. The reaction mixture was heated at about 80° C. for about 3.5 hours, cooled to room temperature and diluted with saturated aqueous $NaHCO_3$ (2 L). The toluene layer was separated and washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated in vacuo to give an oil (754.8 g). Crystallization from methanol/water afforded the desired product as a white solid (609.5 g). ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9H), 2.53 (d, 1H), 2.70 (br, s, 2H), 2.88 (br, s, 1H), 3.31 (m, 2H), 3.97 (m, 1H), 4.19 (m, 1H), 4.46 (br, s, 1H), 4.63 (br, s, 1H), 7.06 (m, 2H), 7.51(m, 1H), 8.34 (m, 1H).

Step C. 3a-Pyridin-2-yl-methyl-2-(2,2,2-trifluoroethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one.



Methanesulfonic acid (11.6 g, 121 mmol) was added dropwise to a solution of the compound prepared according to step B (10 g, 24.2 mmol) in CH_2Cl_2 (100 mL) over about 30 minutes. The reaction mixture was stirred for about 1 hour, then cooled to about 0° C., and then triethylamine (18.6 mL, 133.1 mmol) was added through an addition funnel. The mixture was allowed to warm to room temperature over about 1 hour, diluted with additional CH_2Cl_2 and washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated in vacuo to afford the product as a white solid (7.2 g). ^{1}H-NMR ($CDCl_3$) δ: 2.51–2.72 (m, 4H), 3.35 (m, 2H), 3.49 (m, 2H), 4.03 (m, 1H), 4.25 (m, 1H), 7.08 (d, 2H), 7.51 (t, 1H), 8.37 (d, 1H).

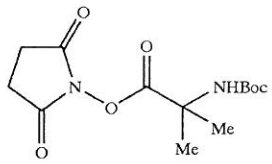
Step D. 3a-Pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one (D)-Tartrate.



In a dry and nitrogen purged 5 L round bottom flask equipped with a mechanical stirrer, D-(−) tartaric acid (129 g, 0.86 mol) was added to the compound prepared according to step C (243 g, 0.78 mol) in acetone/water (9:1, 2430 mL) at about 17° C. The mixture was stirred at room temperature overnight, filtered, the solid was collected and washed with cold acetone and dried under vacuum. The product was obtained as a yellow solid (284 g, yield 78.8%).

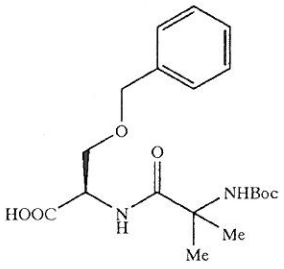
Preparation Three

Step A. 2-tert-Butoxycarbonylamino-2-methyl-propionic Acid 2,5-Dioxo-pyrrolidin-1-yl Ester.



A stirred solution of N-hydroxysuccinimide (112 g, 0.973 mol), N-t-butoxycarbonyl-α-methylalanine (197 g, 0.969 mol), and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (186 g, 0.970 mol) in anhydrous dichloromethane (1.4 L) was stirred at room temperature for about 18 hours under nitrogen atmosphere. The reaction mixture was washed three times each with saturated sodium bicarbonate solution and then brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give the title compound of Step A as a white solid (256 g, 88%): PBMS $(M+18)^+$318; ^{1}H NMR=250 MHz ($CDCl_3$) δ :4.91 (NH, br, s, 1H), 2.84 (—CO(CH_2)$_2$CO—, s, 4H), 1.67 (Me, s, 6H), 1.48 (BOC, s, 9H).

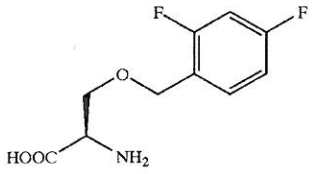
Step B. 2(R)-3-Benzyloxy-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionic Acid.



To a solution of D-O-benzylserine (106 g, 0.532 mol) and the title compound of Step A (160 g, 0.532 mol) in water/dioxane (250/1000 mL) was slowly added triethylamine (223 mL, 1.60 mol) at room temperature. The reaction was heated to about 50° C. and stirred for about 15 hours under nitrogen atmosphere. The solvent was then removed in vacuo, ethyl acetate was added, and the stirred mixture was acidified with 10% aqueous HCl solution to pH 2–3. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give the title compound of Step B (200 g, 99%): -Apcl MS $(M-1)^-$ 379; ^{1}H NMR=300 MHz (methanol-d_4) δ :7.69 (NH, d, 1H), 7.32 (Ph, m, 5H), 4.60 (CHCO$_2$H, m, 1H), 4.51 (CH$_2$Ph, s, 2H), 3.81 (CH$_2$Obz, m, 2H), 1.41 (Me, s, 6H), 1.40 (BOC, s, 9H).

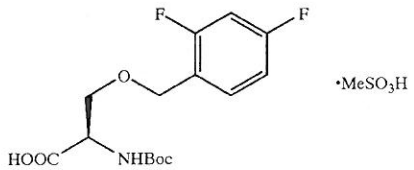
Preparation Four

Step A 2(R)-2-tert-Butoxycarbonylamino-3-(2,4-difluoro-benzyloxy)-propionic Acid.



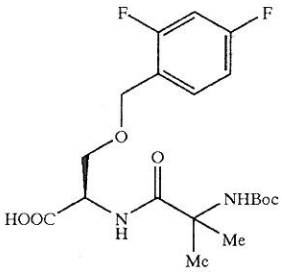
To a solution of N-Boc-(D)-serine (452 g, 2.2026 mol) in a mixture of THF (7 L) and DMF (3 L) at about 0° C. was added potassium tert-butoxide solution (515.8 g, 4.5963 mol). The reaction mixture was stirred at about 0° C. for about 30 min., then 2,4-difluorobenzyl bromide (456.5 g, 2.2051 mol) was added. After warming to room temperature, the reaction mixture was concentrated in vacuo to remove the THF. The reaction mixture was partitioned between 4.5 L H_2O and 4.5 L IPE. The layers were separated and the pH of the aqueous layer was adjusted with 1 N HCl to about 3. The aqueous layer was extracted twice with 4 L each of IPE. The organic solution was dried over Na_2SO_4, and concentrated in vacuo to yield a yellow waxy solid (518.0 g, yield: 70.9%). ^{1}H-NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.73 (m, 1H), 3.94 (d, 1H), 4.44 (br, s, 1H), 4.54 (s, 2H), 5.34 (m, 1H), 6.78 (m, 1H), 6.84 (m, 1H), 7.30 (m, 1H).

Step B. 2(R)-2-Amino-3-(2,4-difluoro-benzyloxy)-propionic Acid, Methanesulfonic Acid Salt.



To a solution of the product from Step A (1.19 g, 3.59 mmol) in CH_2Cl_2/IPE (1:1, 12 mL) was added methanesulfonic acid (1.72 g, 17.95 mmol) through a syringe over about 10 minutes. A solid immediately precipitated out of solution. After about 1 hour, the solid was filtered and washed with a CH_2Cl_2/IPE mixture (1:1) to afford 939 mg of product (yield 80%).

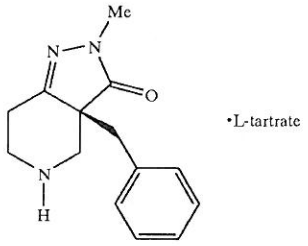
Step C. 2(R)-2-(2-tert-Butoxycarbonylamino-2-methyl-propionylamino)-3-(2,4-difluoro-benzyloxy)-propionic Acid.



To a solution of the product from Step B (520 mg, 1.46 mmol) in THF/water (4:1, 10 mL) was added 2-tert-butoxycarbonylamino-2-methyl-propionic acid-2,5-dioxo-pyrrolidin-1-yl ester (438 mg, 1.46 mmol) and triethylamine (369 mg, 3.65 mmol). The reaction mixture was stirred at room temperature for about 1 hour and quenched with a 10% aqueous citric acid solution (10 mL). After about 15 min., ethyl acetate (50 mL) was added and the organic layer was separated and washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated in vacuo to give a foam (534.1 mg, yield 88%). ^{1}H-NMR (CD_3OD): 61.38 (br, s, 15H), 3.77 (d, 1H), 3.92 (d, 1H), 4.52 (m, 3H), 6.92 (m, 1H), 7.41 (m, 1H), 7.58 (d, 1H).

Preparation Five

(3aR)-2,3a,4,5,6,7-Hexahydro-2-methyl-3a-(Phenylmethyl)-3H-pyrazolo[4,3-c]pyridin-3-one, (2R,3R)-2,3-Dihydroxybutanedioate (1:1)



Step A: 4-oxo-1-(Phenylmethyl)-3-piperidinecarboxylic Acid Methyl Ester, Hydrochloride.

A solution of 1-benzyl4-piperidone (56.5 kg, 1.0 eq.) in toluene (189 L) was prepared at 15° C. to 25° C. A second reactor was charged with toluene (659 L), potassium tert-butoxide (71.9 kg, 2.25 eq.) and dimethyl carbonate (51.5 kg, 2.0 eq.) at 15° C. to 25° C. The resulting slurry was warmed to a temperature of 80° C. to 90° C. The solution of 1-benzyl-4-piperidone in toluene was added slowly to the slurry over 60 to 90 minutes. After an additional 90 minutes, the reaction mixture was cooled to below 15° C. The completed reaction was quenched with acetic acid (38.5 kg, 2.25 eq.) and water (367 L). The two phase mixture was separated. The organic layer was filtered to remove solids. The organic filtrate was concentrated by distillation under reduced pressure to a volume of approximately 150 L. Toluene (799 L) was added to the concentrated mixture. Addition of hydrogen chloride (gas, 11.0 kg, 1.05 eq.) afforded the hydrochloride salt as a precipitate. The slurry was stirred at 10° C. to 15° C. for 30 minutes. The solids were isolated by filtration, washed with approximately hexanes (130 L), and dried using vacuum to give 79.4 kg of 4-oxo-1-(phenylmethyl)-3-piperidinecarboxylic acid methyl ester, hydrochloride (97.8% yield). Analysis calculated for $C_{14}H_{17}NO_3$.HCl: C 59.3; H 6.39; N 4.94; found: C 59.7H, 6.65 N, 4.85.

Step B: 4-oxo-1-Piperidinecarboxylic Acid Methyl ester, Hydrochloride.

Into a clean, dry, nitrogen purged reactor was added 4-oxo-1-(phenylmethyl)-3-piperidinecarboxylic acid methyl ester, hydrochloride (prepared according to Preparation Five, Step A, 78.8 kg, 1.0 eq.), ethanol (416 L), water (340 L), and 10% palladium on carbon (catalyst, 7.88 kg, 0.1 kg/kg). The mixture was subjected to hydrogenation conditions of approximately 45 psig (32×10^3 kg/m^2) of hydrogen pressure at a temperature between 25° C. to 35° C. for approximately 18 hours. After the reaction was complete, the reaction mixture was vented with nitrogen and filtered to removed the spent catalyst. The catalyst cake was washed with ethanol (150 L). The filtrate and washes were concentrated under reduced pressure to approximately 57 L. The product was crystallized by the slow addition of 2-propanol (227 L). The slurry was cooled to 10° C. to 20° C. and stirred for approximately one hour. The product was isolated by filtration, rinsed with hexanes (76 L), and dried under vacuum for approximately 24 hours to give 43.2 kg 4-oxo-1-piperidinecarboxylic acid methyl ester, hydrochloride (80.0% yield). Analysis calculated for $C_7H_{11}NO_3$.HCl: C 43.42; H 6.25; N 7.23; found: C 43.7; H 6.59; N 7.19.

Step C: 4-oxo-1,3-Piperidinecarboxylic Acid 1-(1,1-Dimethylethyl) 3-Methyl Ester.

A clean, dry, nitrogen purged, glass-lined vessel was charged with isopropyl ether (IPE, 309 L), 4-oxo-1-piperidinecarboxylic acid methyl ester, hydrochloride (prepared according to Preparation Five, Step B, 42.6 kg, 1.0 eq.), and water (153 L) at 15 to 25° C. Addition of triethylamine (28.9 kg, 1.3 eq.) resulted in a thick white emulsion. Slow addition of di-tert-butyldicarbonate (52.6 Kg, 50 L, 1.1 eq.) to the reaction mixture, followed by an IPE rinse, resulted in a clear biphasic solution. The mixture was agitated at 15° C. to 25° C. for about 12 hours. After reaction completion, the aqueous layer was separated off and extracted with IPE (20 L). The organic extracts were combined and washed sequentially with 1N HCl (110 L), water (90 L), and saturated sodium chloride solution (103 L). The washed organic layer was dried over anhydrous sodium sulfate. The mixture was filtered to remove insolubles. The filtrate was concentrated using vacuum distillation to give the oil 4-oxo-1,3-piperidinedicarboxylic acid 1-(1,1-dimethylethyl) 3-methyl ester. About 49 L (53 kg) of product oil (assumed 95% yield) was collected. The oil was held in the reactor for immediate use in the next step.

Step D: 4-oxo-3-(Phenylmethyl)-1,3-piperidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 3-Methyl Ester.

The nitrogen purged vessel containing about 4-oxo-1,3-piperidinedicarboxylic acid 1-(1,1-dimethylethyl) 3-methyl ester (prepared according to Preparation Five, Step C, 53 kg, 49 L, 1.0 eq.) was charged with tetrahydrofuran (THF, 536 L) and potassium carbonate (72 kg, 2.5 eq.). The slurry was treated with benzyl bromide (36.0 kg, 1.01 eq.) over 10 to 15 minutes. The reaction mixture was heated at reflux temperature until reaction was complete (generally between 12 and 18 hours). The mixture was cooled to between 20° C. and 25° C., filtered to remove the salts, and the filter cake washed with THF (134 L). The THF was removed from the mixture by partial vacuum distillation and replaced with heptanes (402 L). The resulting slurry was cooled to between −5° C. and 5° C. and stirred for about one hour. The

solids were collected by filtration, washed with heptanes (57 L) cooled between 0° C. to 10° C., and dried under vacuum between 45° C. to 55° C. to give 50.1 kg of 4-oxo-3-(phenylmethyl)-1,3-piperidinedicarboxylic acid 1-(1,1-dimethylethyl) 3-methyl ester (69.2% yield). HPLC assay showed a product peak of 99.2% at about 12 minutes. HPLC conditions: Intersil C-8 column, 4.6×150 mm; mobile phase: 50%acetonitrile/water; aqueous phase: 1 L water, 3 mL triethylamine and 1 mL H_3PO_4 at pH 6.5; flow rate 1.0 mL/min.; detected by UV at 210 nm.

Step E: 2,3,3a,4,6,7-Hexahydro-2-methyl-3-oxo-3a-(Dhenylmethyl)-5H-pyrazolo[4,3-c]pyridine-5-carboxylic Acid 1,1-Dimethylethyl Ester.

Methylhydrazine is highly toxic, is a cancer suspect agent, is flammable and is potentially explosive. It should be handled with extreme care. Have spill kits, drying agents, liqua paks and fire extinguishers on hand during handling. Ensure air hoses are long enough to escape any accident scene. Since methylhydrazine can react with metal oxides, the reaction vessel was inspected to ensure that no metal surfaces were exposed prior to initiating the reaction. In a clean, glass-lined, nitrogen purged vessel, 4-oxo-3-(phenylmethyl)-1,3-piperidinedicarboxylic acid 1-(1,1-dimethylethyl) 3-methyl ester (prepared according to Preparation Five, Step D, 50.1 kg, 1.0 eq.) was dissolved in methyl-t-butyl ether (MTBE, 208 L) at 15° C. to 20° C. to form a solution. The reaction solution was charged with methylhydrazine (7.6 kg, 1.15 eq.). After stirring for about 30 minutes, acetic acid (13.0 kg, 1.5 eq.) was added. The reaction mixture was slowly heated to reflux temperature (53° C. to 57° C.) and held at reflux for 15 to 20 hours. The reaction was cooled to between 20° C. and 25° C. The reaction mixture was cooled to between 5° C. and 10° C. and slowly charged with 10% sodium bicarbonate solution in water (175 L). The biphasic mixture was separated and the organic layer was washed sequentially with water (175 L) and saturated sodium chloride solution (175 L). The aqueous wash layers should be combined and treated with bleach solution to destroy any residual methylhydrazine prior to disposal. The organic solution was concentrated to a volume between 130 and 170 L under partial vacuum. Addition of heptanes (174 L) to the mixture precipitated the product. The slurry was stirred for 2 hours at a temperature between 5° C. and 10C. The solids were isolated by filtration, washed with cold MTBE (34 L), and dried under vacuum at a temperature between 35° C. and 45° C. for 24 hours to give 47.1 kg of 2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid 1,1-dimethylethyl ester (95.1% yield). HPLC assay showed a product peak of 99.1% at about 5 minutes. HPLC conditions: Intersil C-8 column, 4.6×150 mm; mobile phase: 50%acetonitrile/water; aqueous phase: 1 L water, 3 mL triethylamine and 1 mL H_3PO_4 at pH 6.5; flow rate 1.0 mL/min.; detected by UV at 205 nm.

Step F: (3aR)-2,3a,4,5,6,7-Hexahydro-2-methyl-3a-(phenylmethyl)-3H-pyrazolo[4,3-c]pyridin-3-one, (2R,3R)-2,3-Dihydroxybutanedioate (1:1).

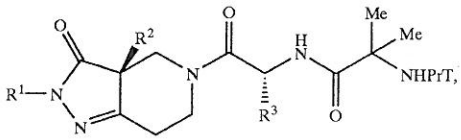
It has been observed that the intermediate free amine epimerizes in solution and as an isolated solid. Therefore, the dynamic resolution step was completed immediately following the deprotection step. A clean, nitrogen purged reactor was charged with methylene chloride (471 L) and 2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid 1,1-dimethylethyl ester (prepared according to Preparation Five, Step E, 47.0 kg, 1.0 eq.). The mixture was agitated and cooled to between −5° C. and 5° C. The reaction mixture was slowly charged with triflouroacetic acid (117 kg, 7.5 eq.). The reaction mixture was warmed to a temperature between 20° C. and 30° C. and stirred for 12 to 15 hours. The reaction mixture was quenched by slow addition of an aqueous solution of 10% sodium carbonate (486 L, 0.5 eq.) at a temperature between 5° C. and 15° C. The organic layer was separated and the aqueous layer extracted with methylene chloride (19 L).

A mixture of acetone (456 L), water (56.4 L), and L-tartaric acid (22.6 kg, 1.1 eq.) was prepared in a second reactor. The tartaric acid mixture was combined with the organic layers at a temperature between 20° C. and 25° C. The resulting slurry was heated to a temperature between 35° C. and 45° C. and stirred for 8 to 18 hours (overnight). When the reaction was judged to be complete, the slurry was cooled and granulated at a temperature between 0° C. and 10° C. for three to four hours and filtered. The product cake was washed with a mixture of acetone (40 L) and water (4.5 L). The product was dried under vacuum using only mild heat (applied if evaporation of acetone results in cooling). A yield of 37.7 kg of (3aR)-2,3a,4,5,6,7-hexahydro-2-methyl-3a-(phenylmethyl)-3H-pyrazolo[4,3-c]pyridin-3-one, (2R,3R)-2,3-dihydroxybutanedioate (1:1) was obtained (70.1% yield).

What is claimed is:

1. A process of preparing a compound of Formula II,

II



wherein:

R^1 is —(C_1–C_{10})alkyl optionally substituted with up to three fluoro atoms;

R^2 is phenylmethyl or 2-pyridylmethyl;

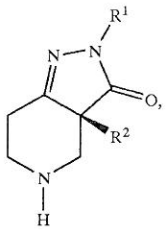
R^3 is —(C_1–C_5)alkyl-O—(C_0–C_5)alkylphenyl, where the phenyl substituent in the definition of R^3 is optionally substituted with up to three fluoro atoms; and

Prt is an amine protecting group,

comprising:

a) mixing an appropriate chiral tartrate salt having the structure of Formula IV,

IV



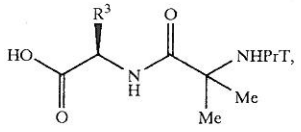
D- or L-tartaric acid

wherein R^1 and R^2 are as defined above,

and an organic amine in a reaction inert solvent at a temperature of about −68° C. to about −40° C. to form a slurry;

b) adding a compound of the Formula V,

V



wherein R^3 and Prt are as defined above,

to said slurry to form a reaction mixture comprising the tartrate salt of the organic amine, the free base of a compound of Formula IV and a compound of the formula V; and

c) adding a coupling reagent to said reaction mixture to form a compound of Formula II.

2. A process of claim **1** wherein said compound of Formula IV is suspended in said solvent prior to the addition of said organic amine.

3. A process of claim **2** wherein said slurry is warmed to about −50° C. prior to step b.

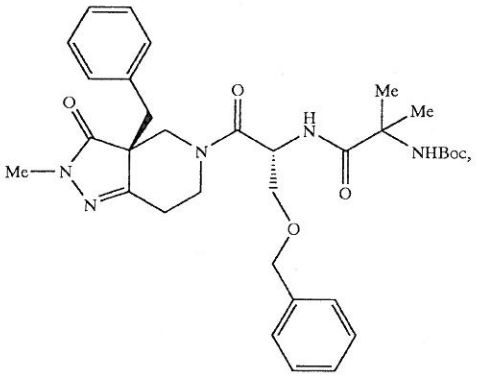
4. A process of claim **1** wherein: in step a, said organic amine is triethylamine; in step b, R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl and Prt is tert-butyloxycarbonyl; and in step c, said coupling reagent is propane phosphonic acid anhydride.

5. A process of claim **4** wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

6. A process of claim **5** wherein the compound of Formula II selected from (1-(2-(1(R)-(2,4-difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester and (1-(2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester is prepared.

7. A process of claim **5** wherein a compound of Formula IIA,

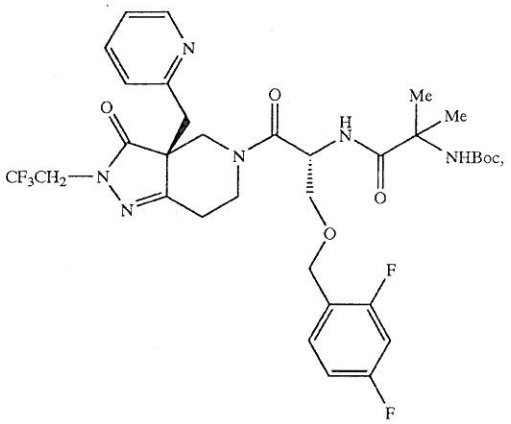
IIA



wherein Boc is tert-butloxycarbonyl, is prepared.

8. A process of claim **5** wherein a compound of Formula IIB,

IIB



wherein Boc is tert-butyloxycarbonyl, is prepared.

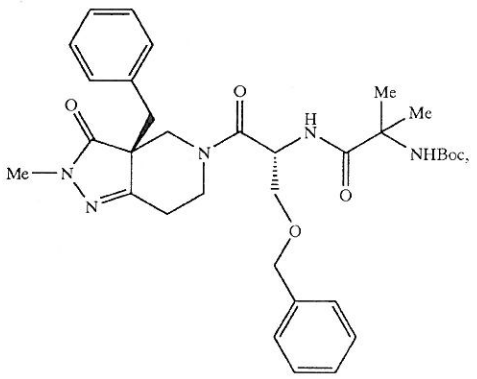
9. A process of claim **2** wherein: in step a, said organic amine is triethylamine; in step b, R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl and Prt is tert-butyloxycarbonyl; and in step c, said coupling reagent is propane phosphonic acid anhydride.

10. A process of claim **9** wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

11. A process of claim **10** wherein the compound of Formula II selected from (1-(2-(1(R)-(2,4-difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester and (1-(2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester is prepared.

12. A process of claim **10** wherein a compound of Formula IIA,

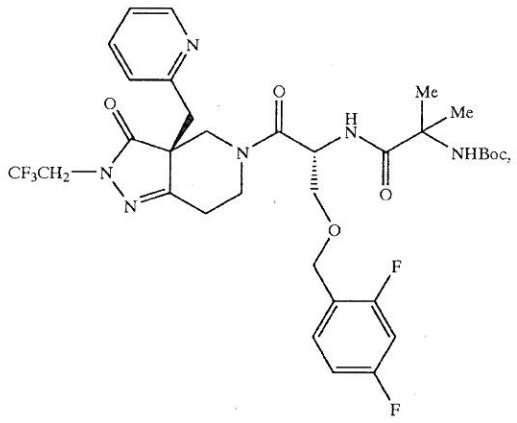
IIA



wherein Boc is tert-butyloxycarbonyl, is prepared.

13. A process of claim 10 wherein a compound of Formula IIB,

IIB



wherein Boc is tert-butyloxycarbonyl, is prepared.

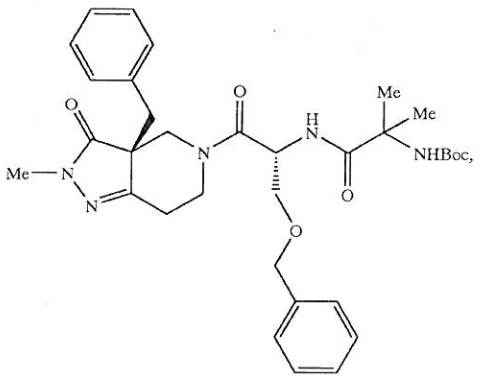
14. A process of claim 3 wherein: in step a, said organic amine is triethylamine; in step b, R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl and Prt is tert-butyloxycarbonyl; and in step c, said coupling reagent is propane phosphonic acid anhydride.

15. A process of claim 14 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

16. A process of claim 15 wherein the compound of Formula II selected from (1-(2-(1(R)-(2,4-difluorobenzyloxymethyl)-3a(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester and (1-(2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester is prepared.

17. A process of claim 15 wherein a compound of Formula IIA,

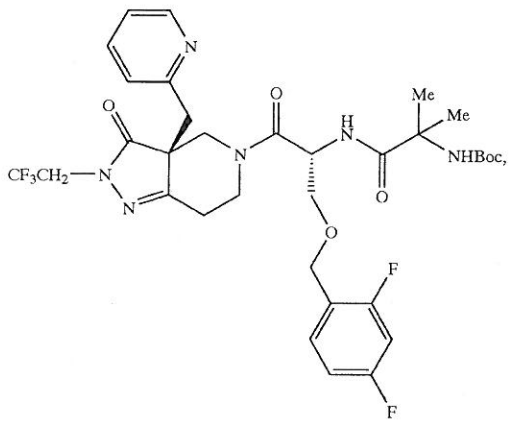
IIA



wherein Boc is tert-butyloxycarbonyl is prepared.

18. A process of claim 15 wherein a compound of Formula IIB,

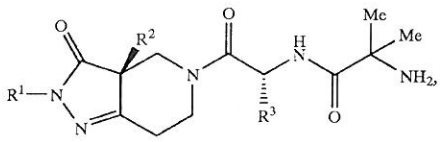
IIB



wherein Boc is tert-butyloxycarbonyl is prepared.

19. A process for preparing a compound of Formula III,

III



wherein:

R^1 is —(C_1–C_{10})alkyl optionally substituted with up to three fluoro atoms;

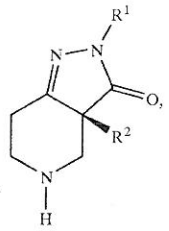
R^2 is phenylmethyl or 2-pyridylmethyl; and

R^3 is —(C_1–C_5)alkyl-O—(C_0–C_5)alkylphenyl, where the phenyl substituent in the definition of R^3 is optionally substituted with up to three fluoro atoms,

comprising:

a) mixing an appropriate chiral tartrate salt having the structure of Formula IV,

IV



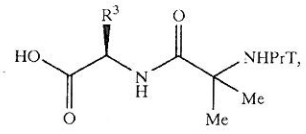
D- or L-tartaric acid

wherein R^1 and R^2 are as defined above,

and an organic amine in a reaction inert solvent at a temperature of about −68° C. to about −45° C. to form a slurry;

b) adding a compound of the Formula V,

V



wherein R^3 is as defined above and Prt is an amine protecting group, to said slurry to form a reaction mixture comprising the tartrate salt of the organic amine, the free base of a compound of Formula IV and a compound of the Formula V;

c) adding a coupling reagent to said reaction mixture to form a compound of Formula II; and

d) reacting said compound of Formula II with a suitable deprotecting reagent to form a compound of Formula III.

20. A process of claim **19** wherein said compound of Formula IV is suspended in said solvent prior to the addition of said organic amine comprising the additional step of warming said slurry to about −50° C. to about −40° C. prior to step b.

21. A process of claim **20** wherein said Prt is tert-butyloxycarbonyl and said tert-butyloxycarbonyl is removed by reacting said compound of Formula II with an acid.

22. A process of claim **21** wherein said acid is methanesulfonic acid.

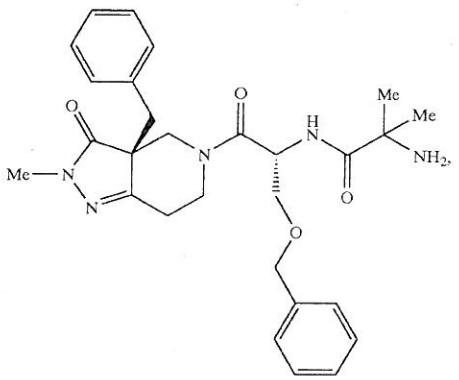
23. A process of claim **22** wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

24. A process of claim **23** wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

25. A process of claim **24** wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c] pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

26. A process of claim **24** wherein a compound of formula IIIA,

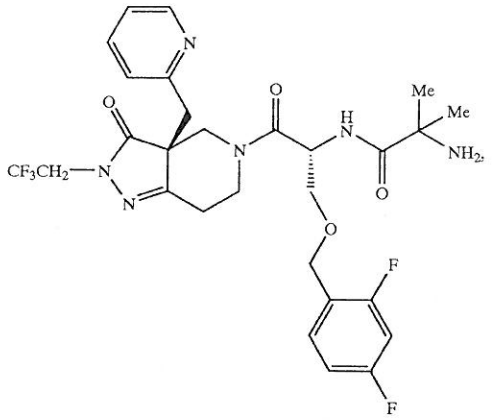
IIIA



is prepared.

27. A process of claim **24** wherein a compound of formula IIIB,

IIIB



is prepared.

28. A process of claim **21** wherein said acid is trifluoroacetic acid.

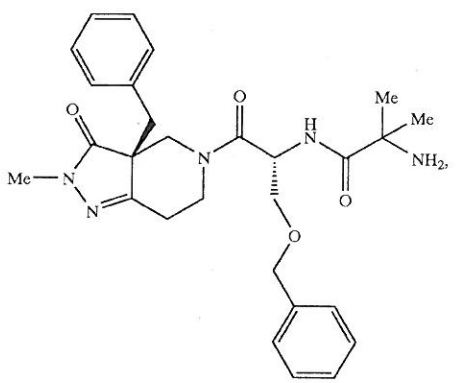
29. A process of claim **28** wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step c, said coupling reagent is propane phosphonic acid anhydride.

30. A process of claim **29** wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

31. A process of claim **30** wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c] pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide is prepared.

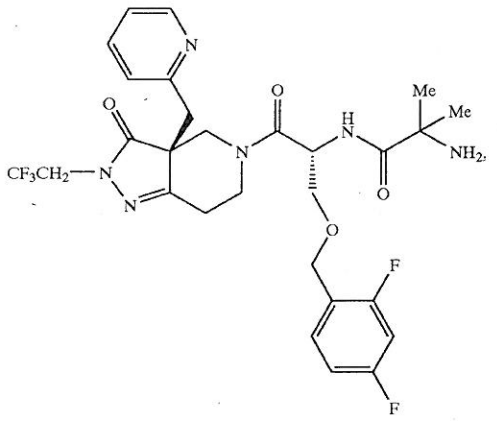
32. A process of claim **30** wherein a compound of formula IIIA,

IIIA



is prepared.

33. A process of claim 30 wherein a compound of formula IIIB,



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is prepared.

34. A process of claim 19 wherein said Prt is tert-butyloxycarbonyl and said tert-butyloxycarbonyl is removed by reacting said compound of Formula II with an acid.

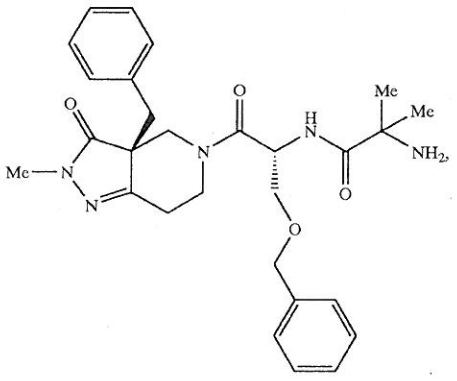
35. A process of claim 34 wherein said acid is methanesulfonic acid.

36. A process of claim 35 wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step f, said coupling reagent is propane phosphonic acid anhydride.

37. A process of claim 36 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

38. A process of claim 37 wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c] pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide.

39. A process of claim 37 wherein a compound of formula IIIA,



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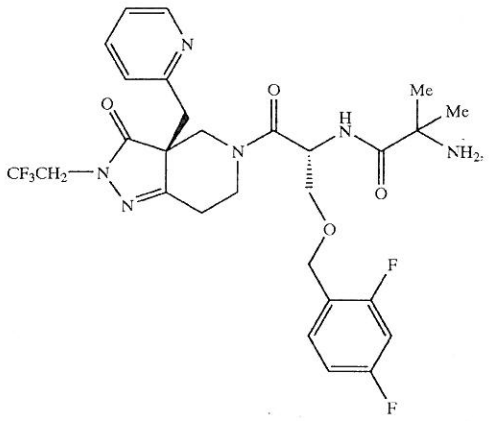
is prepared.

40. A process of claim 37 wherein a compound of formula IIIB,



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is prepared.

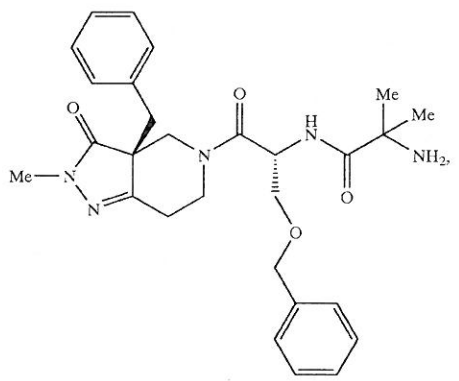
41. A process of claim 34 wherein said acid is trifluoroacetic acid.

42. A process of claim 41 wherein: R^3 is phenylmethyloxymethyl or 2,4-difluorophenylmethyloxymethyl; in step b, said organic amine is triethylamine; and in step f, said coupling reagent is propane phosphonic acid anhydride.

43. A process of claim 42 wherein R^1 is methyl or 2,2,2-trifluoroethyl and R^2 is phenylmethyl or 2-pyridylmethyl.

44. A process of claim 43 wherein said compound of Formula III selected from 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c] pyridin-5-yl-1(R)-benzyloxylmethyl-2-oxo-ethyl]-isobutyramide and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl-2-methyl-propionamide.

45. A process of claim 43 wherein a compound of formula IIIA,

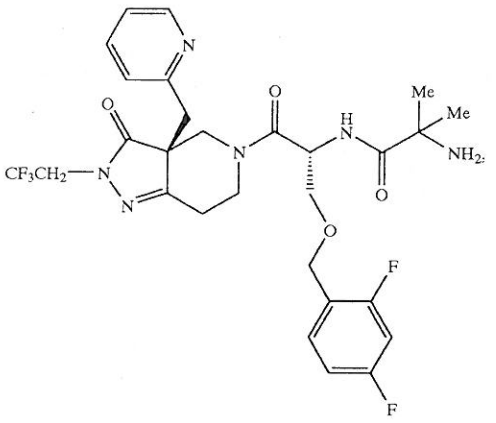


IIIA

is prepared.

46. A process of claim 43 wherein a compound of formula IIIB,

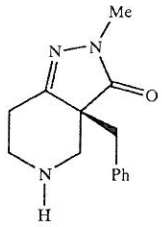
IIIB



is prepared.

47. A polymorph of a dihydrate of a compound of formula XX:

XX



•L-tartrate.

48. A polymorph of claim 47 having the X-Ray crystal structure according to FIG. 1.

49. A polymorph of claim 47 having the atomic coordinates and equivalent isotropic displacement coefficients as set forth in Table II:

TABLE II

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$)

	x	y	z	U(eq)
C(1')	7050 (7)	12045 (7)	6424 (4)	31(1)
O(1A')	5715 (5)	12748 (6)	6097 (3)	41(1)
O(1B')	8234 (5)	12946 (6)	6748 (3)	41(1)
C(2')	7120 (6)	9881 (7)	6388 (4)	29(1)
O(2')	8733 (5)	9232 (6)	6715 (3)	37(1)
C(3')	6707 (7)	9167 (7)	5599 (4)	32(1)
O(3')	7899 (5)	9726 (6)	5160 (3)	47(1)
C(4')	6647 (7)	6999 (7)	5583 (4)	32(1)
O(4A')	5644 (5)	6263 (6)	5971 (3)	39(1)
O(4B')	7465 (5)	6110 (7)	5213 (3)	59(1)
N(1)	5011 (6)	8379	1995 (3)	43(1)
N(2)	4317 (6)	6558 (7)	1896 (3)	40(1)
C(2A)	2623 (6)	6380 (8)	1541 (4)	55(1)
C(3)	5357 (7)	5149 (8)	2171 (4)	36(1)
O(3)	5039 (5)	3491 (6)	2188 (3)	46(1)
C(4)	6998 (6)	6172 (8)	2450 (3)	28(1)
C(5)	6515 (6)	8177 (8)	2299 (4)	33(1)
C(6)	7511 (6)	5878 (8)	3290 (4)	39(1)
N(7)	8723 (6)	7355 (7)	3591 (3)	40(1)
C(8)	8153 (7)	9366 (8)	3440 (4)	49(1)
C(9)	7643 (7)	9700 (8)	2603 (4)	46(1)
C(10)	8290 (6)	5440 (8)	1989 (4)	37(1)
C(11)	7862 (7)	5776 (8)	11667 (4)	43(1)
C(12)	8463 (7)	7317 (8)	853 (4)	69(1)
C(13)	8108 (8)	7675 (9)	76 (5)	97(1)
C(14)	7080 (*)	6405 (9)	−336 (5)	96(1)
C(15)	6443 (8)	4882 (8)	−59 (5)	81(1)
C(16)	6872 (7)	4533 (8)	705 (4)	75(1)
O(1W)	8100 (5)	6278 (7)	7609 (3)	54(1)
O(2W)	10828 (5)	8138 (7)	5099 (3)	62(1)

50. A polymorph of claim 49 further having the bond lengths as set forth in Table III:

TABLE III

Bond Lengths (Å)

C(1')–O(1A')	1.262(7)	C(1')–O(1B')	1.229 (7)
(C1')–C(2')	1.525(7)	C(2')–O(2')	1.4347 (6)
C(2')–C(3')	1.500(9)	C(3')–O(3')	1.416 (8)
C(3')–C(4')	1.526(7)	C(4')–O(4A')	1.277 (8)
C(4')–O(4B')	1.201(8)	N(1)–N(2)	1.402 (5)
N(1)–C(5)	1.278(7)	N(2)–C(2A)	1.443 (7)
N(2)–C(3)	1.350(7)	C(3)–O(3)	1.196 (7)
C(3)–C(4)	1.541(7)	C(4)–C(5)	1.478 (7)
C(4)–C(6)	1.526(9)	C(4)–C(10)	1.544 (9)
C(5)–C(9)	1.465(7)	C(6)–N(7)	1.481 (7)
N(7)–C(8)	1.501(7)	C(8)–C(9)	1.524 (10)
C(10)–C(11)	1.492(9)	C(11)–C(12)	1.355 (9)
C(11)–C(16)	1.380(8)	C(12)–C(13)	1.411 (12)
C(13)–C(14)	1.365(9)	C(14)–C(15)	1.327 (10)
C(15)–C(16)	1.393(11)		

51. A polymorph of claim 50 further having the bond angles as set forth in Table IV:

TABLE IV

Bond Angles (°)

O(1A')–C(1')–O(1B')	125.8(5)	O(1A')–C(1')–C(2')	114.1(5)
O(1B')–C(1')–C(2')	120.2(5)	C(1')–C(2')–O(2')	109.8(4)
C(1')–C(2')–C(3')	111.7(5)	O(2')–C(2')–C(3')	109.7(5)
C(2')–C(3')–O(3')	111.9(4)	C(2')–C(3')–C(4')	110.7(5)
O(3')–C(3')–C(4')	106.9(5)	C(3')–C(4')–O(4A')	114.6(5)
C(3')–C(4')–O(4B')	120.7(6)	O(4A')–C(4')–O(4B')	124.6(5)
N(2)–N(1)–C(5)	107.4(3)	N(1)–N(2)–C(2A)	118.7(4)
N(1)–N(2)–C(3)	113.8(4)	C(2A)–N(2)–C(3)	127.5(5)
N(2)–C(3)–O(3)	126.6(5)	N(2)–C(3)–C(4)	104.3(4)
O(3)–C(3)–C(4)	129.0(5)	C(3)–C(4)–C(5)	100.9(4)
C(3)–C(4)–C(6)	110.4(5)	C(5)–C(4)–C(6)	109.6(5)
C(3)–C(4)–C(10)	108.2(5)	C(5)–C(4)–C(10)	114.0(5)
C(6)–C(4)–C(10)	113.0(4)	N(1)–C(5)–C(4)	113.4(4)
N(1)–C(5)–C(9)	126.2(4)	C(4)–C(5)–C(9)	119.5(4)
C(4)–C(6)–N(7)	109.4(5)	C(6)–N(7)–C(8)	115.0(4)
N(7)–C(8)–C(9)	110.7(5)	C(5)–C(9)–C(8)	108.4(5)
C(4)–C(10)–C(11)	114.5(4)	C(10)–C(11)–C(12)	120.2(5)
C(10)–C(11)–C(16)	121.6(6)	C(12)–C(11)–C(16)	118.3(7)
C(11)–C(12)–C(13)	122.0(6)	C(12)–C(13)–C(14)	115.9(7)
C(13)–C(14)–C(15)	124.7(8)	C(14)–C(15)–C(16)	117.8(6)
C(11)–C(16)–C(15)	121.2(6)		

52. A polymorph of claim 51 further having the anisotropic displacement coefficients as set forth in Table V:

TABLE V

	Anisotropic displacement coefficients ($Å^2 \times 10^3$)					
	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1')	32 (1)	26 (1)	34(1)	2 (1)	5 (1)	-8 (1)
O(1A')	35 (1)	19 (1)	67(1)	-4 (1)	2 (1)	2 (1)
O(1B')	35 (1)	26 (1)	60(1)	-4 (1)	-2 (1)	-13 (1)
C(2')	32 (1)	17 (1)	36(1)	1 (1)	-1 (1)	1 (1)
O(2')	32 (1)	33 (1)	43(1)	4 (1)	-1 (1)	0 (1)
C(3')	41 (1)	18 (1)	37(1)	6 (1)	6 (1)	-6 (1)
O(3')	71 (1)	33 (1)	41(1)	-2 (1)	23 (1)	1 (1)
C(4')	28 (1)	27 (1)	39(1)	2 (1)	3 (1)	2 (1)
O(4A')	41 (1)	32 (1)	45(1)	-7 (1)	10 (1)	-9 (1)
O(4B')	56 (1)	35 (1)	92(1)	7 (1)	32 (1)	-2 (1)
N(1)	39 (1)	48 (1)	37(1)	4 (1)	-6 (1)	7 (1)
N(2)	30 (1)	39 (1)	47(1)	2 (1)	-2 (1)	-4 (1)
C(2A)	27 (1)	66 (1)	68(1)	-3 (1)	-2 (1)	-1 (1)
C(3)	39 (1)	40 (1)	30(1)	8 (1)	10 (1)	-7 (1)
O(3)	45 (1)	27 (1)	65(1)	-3 (1)	5 (1)	1 (1)
C(4)	23 (1)	34 (1)	26(1)	0 (1)	2 (1)	3 (1)
C(5)	31 (1)	32 (1)	36(1)	-1 (1)	6 (1)	0 (1)
C(6)	38 (1)	38 (1)	38(1)	4 (1)	1 (1)	-4 (1)
N(7)	39 (1)	42 (1)	34(1)	1 (1)	-6 (1)	-1 (1)
C(8)	44 (1)	46 (1)	54(1)	-1 (1)	1 (1)	-9 (1)
C(9)	41 (1)	42 (1)	52(1)	6 (1)	2 (1)	0 (1)
C(10)	37 (1)	46 (1)	29(1)	6 (1)	9 (1)	4 (1)
C(11)	39 (1)	55 (1)	37(1)	10 (1)	7 (1)	-2 (1)
C(12)	72 (1)	85 (1)	49(1)	4 (1)	2 (1)	1 (1)
C(13)	103 (1)	108 (1)	82(1)	2 (1)	16 (1)	27 (1)
C(14)	103 (1)	108 (1)	73(1)	13 (1)	4 (1)	6 (1)
C(15)	81 (1)	93 (1)	63(1)	-4 (1)	-6 (1)	-17 (1)
C(16)	80 (1)	88 (1)	58(1)	-4 (1)	13 (1)	-12 (1)
O(1W)	56 (1)	45 (1)	60(1)	-7 (1)	7 (1)	-2 (1)
O(2W)	58 (1)	48 (1)	91(1)	3 (1)	42 (1)	7 (1)

53. A polymorph of claim 52 further having the hydrogen atom coordinates and isotropic displacement coefficients as set forth in Table VI:

TABLE VI

	H-Atom coordinates ($\times 10^4$) and isotropic displacement coefficients ($Å^2 \times 10^3$)			
	x	y	z	U
H(2')	6314	9385	6665	80
H(2A')	8195 (10)	8867 (10)	7105 (9)	50
H(3')	5656	9704	5398	80
H(3A')	8259 (10)	11720 (10)	5037 (9)	50
H(4A')	5234 (10)	6488 (10)	6270 (9)	50
H(2A)	2319	5061	1512	80
H(2B)	2495	6907	1046	80
H(2C)	1928	7053	1829	80
H(6A)	7999	4642	3381	80
H(6B)	6562	5972	3533	80
H(7A)	9771 (10)	7980 (10)	3431 (9)	50
H(7B)	9183 (10)	7721 (10)	4160 (9)	50
H(8A)	7229	9605	3689	80
H(8B)	9033	10220	3630	80
H(9A)	8599	9685	2362	80
H(9B)	7101	10908	2520	80
H(10A)	8417	4095	2071	80
H(10B)	9315	6067	2166	80
H(12)	9152	8192	1169	80
H(13)	8559	8747	-149	80
H(14)	6799	6628	-864	80
H(15)	5710	4049	-375	80
H(16)	6471	3406	915	80
H(1WA)	8471 (10)	5946 (10)	7323 (9)	52(1)
H(1WB)	6863 (10)	5969 (10)	7529 (9)	50
H(2WA)	11347 (10)	8095 (10)	5456 (9)	50
H(2WB)	11515 (10)	9176 (10)	4829 (9)	50

* * * * *

EXHIBIT 6

United States Patent and Trademark Office

Patent Bibliographic Data					03/29/2016 09:39 AM
Patent Number:	6673929		**Application Number:**	10283720	
Issue Date:	01/06/2004		**Filing Date:**	10/30/2002	
Title:	PROCESS FOR PREPARING GROWTH HORMONE SECRETAGOGUES				
Status:	4th, 8th and 12th year fees paid			**Entity:**	LARGE
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	07/06/2015 07/06/2011 06/21/2007 12/29/2003	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. Payor Number Assigned. --- End of Maintenance History ---			
Address for fee purposes:	PHARMACIA CORPORATION c/o Pfizer Inc. Attn:Legal Patent Department, Chief IP C 235 East 42nd Street New York NY 10017				

Run Another Query

EXHIBIT 7

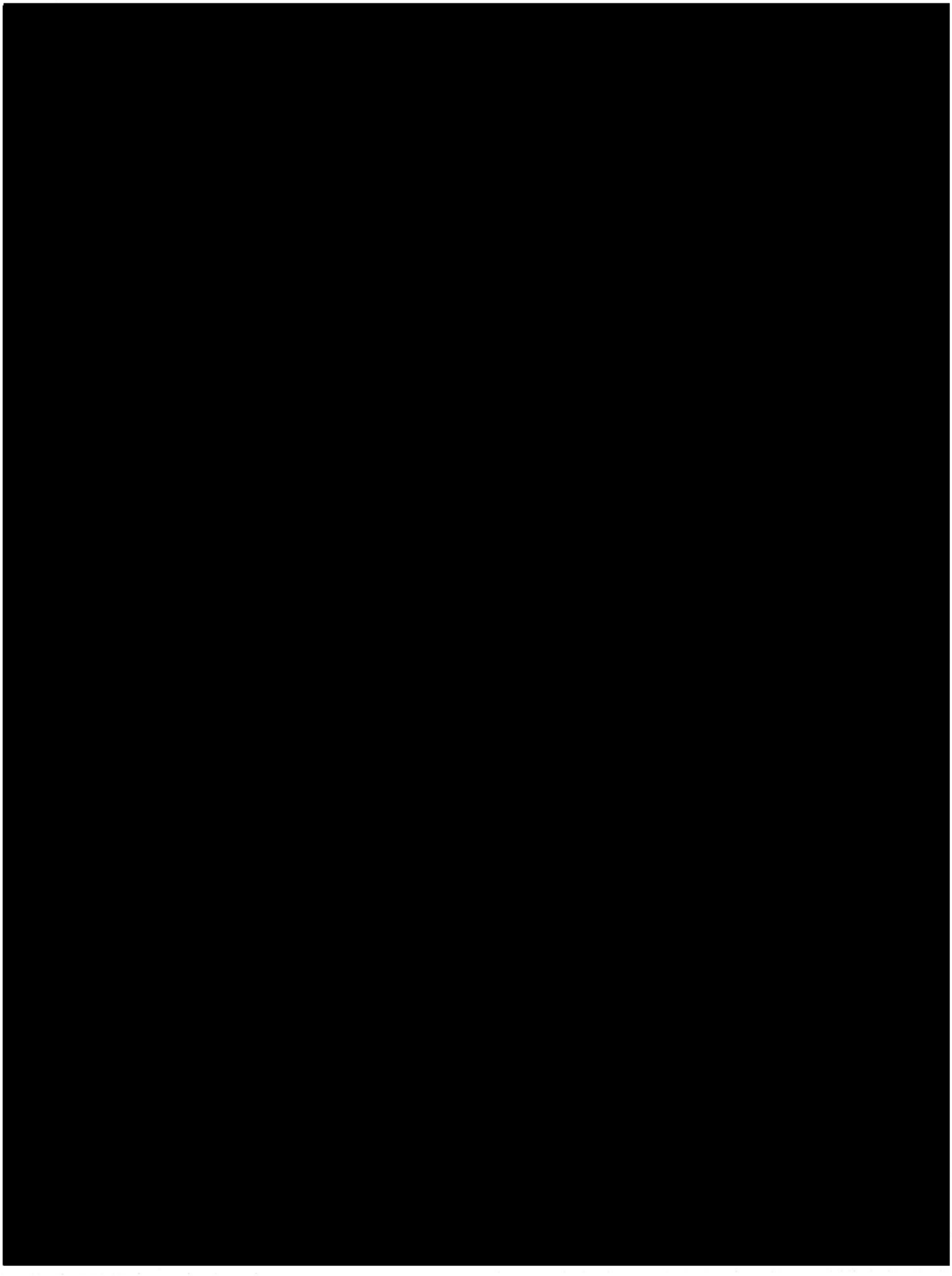


EXHIBIT 8

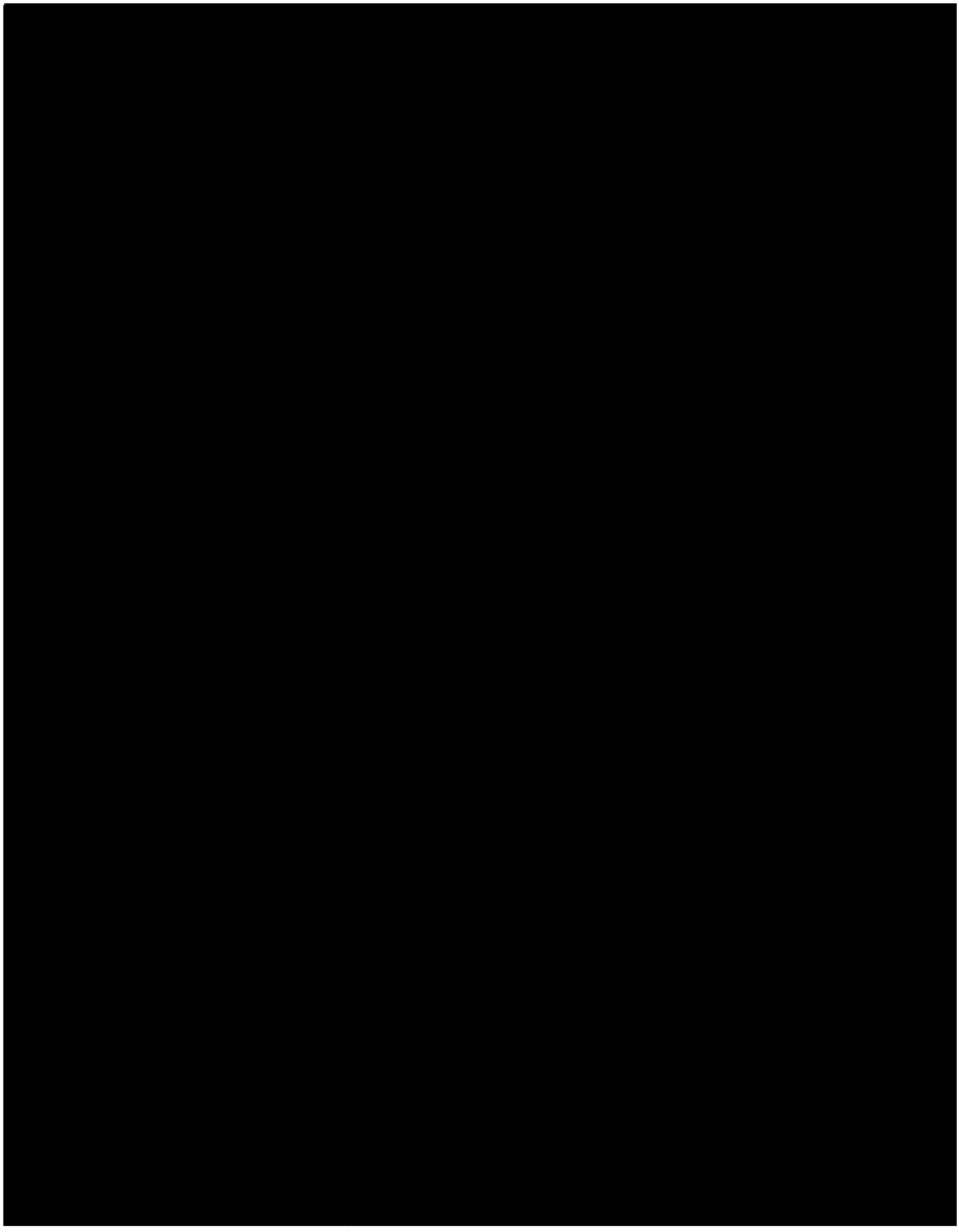


EXHIBIT 9

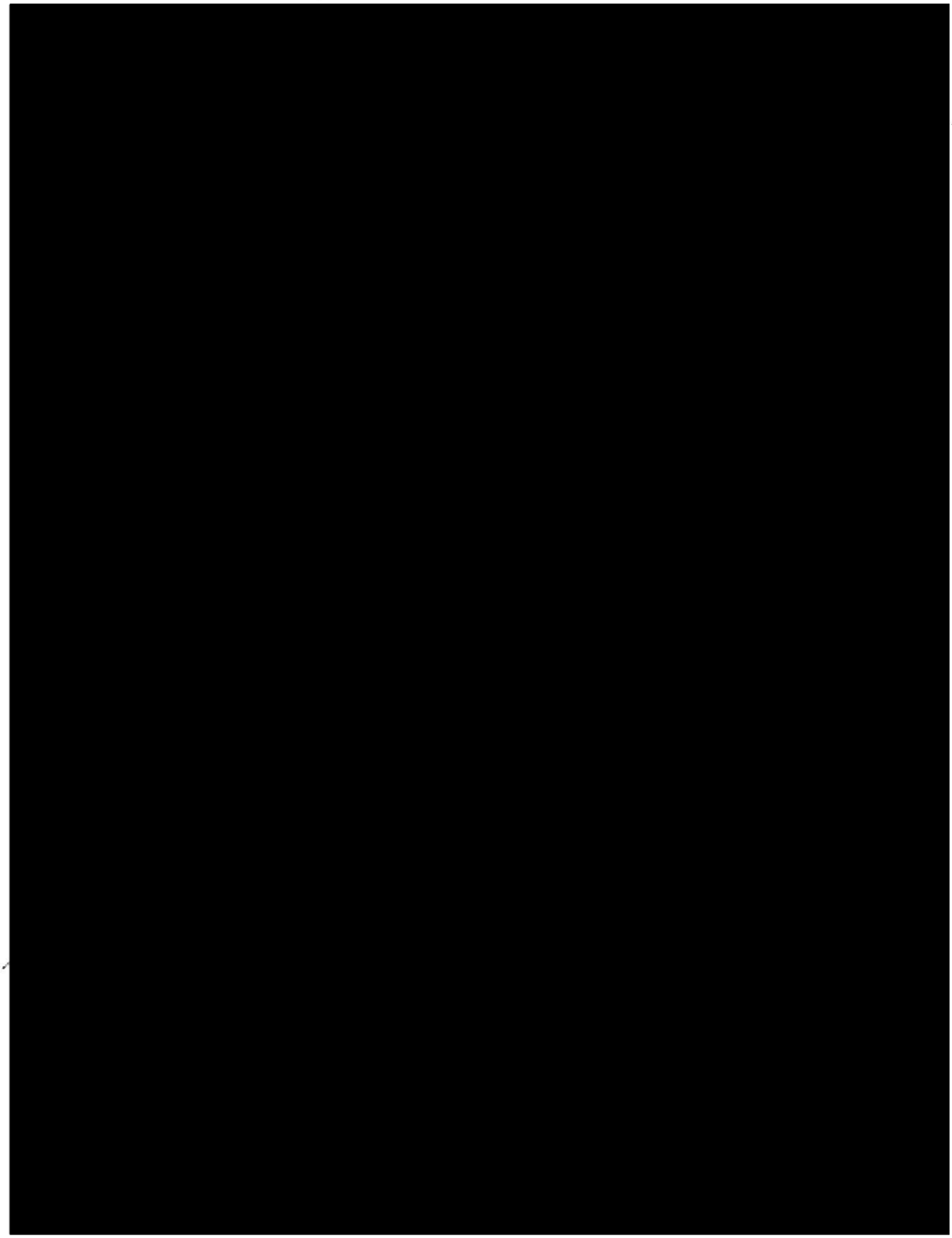


EXHIBIT 10

November 1, 2011

Dr. Steven Fleischer
Acting Director
Division of Therapeutic Drugs for Non-Food Animals (HFV-110)
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: Request for Establishment of an Investigational New Animal Drug (INAD) File

Dear Dr. Fleischer:

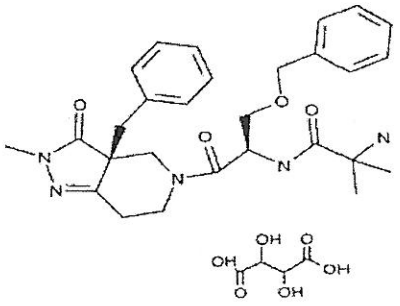
This letter requests that CVM open an INAD on behalf on Artana Therapeutics, Inc. (the Sponsor) for the ghrelin-like drug described below to be used to increase food intake/appetite in dogs with disease conditions or frailty that lead to inappetence/anorexia. In the near future, we intend to submit background information and request a series of pre-submission meetings to educate and then discuss the development plan of this drug compound.

Please Note: Aratana Therapeutics is the sponsor of INAD 011-093 – for the same drug compound in cats. INAD 011-093 was originally established for Pfizer in March 2003 and then transferred to Aratana Therapeutics per request dated June 8, 2011 and verified by a CVM letter dated July 7, 2011.

Preliminary information concerning this drug compound is provided below:

COMPOUND:

Structure:



Code Numbers: CP-424,391 and AT-002

Molecular Weight: 655.70 Daltons

Molecular Formula: $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_6$

Chemical Name: 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5- yl)-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartrate

CLASS OF DRUG: Ghrelin-like, Growth Hormone Secretagogue

SPECIES: Dogs

PROPOSED INDICATIONS: To increase food intake/appetite in dogs with disease conditions or frailty that leads to inappetence/anorexia.

PROPOSED DOSAGE FORM: Oral Liquid or Solid-Dose Tablet

Please call me at 913-424-4714 or contact me by email at bzollers@aratanarx.com if you have any questions or need further information.

Regards,

Bill Zollers, PhD
Vice President – Drug Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

INAD 012-103

November 02, 2011

Aratana Therapeutics, Inc
Attention: Bill Zollers, PhD
Vice President – Drug Development
1901 Olathe Blvd,
Kansas City, KS 66103

Dear Dr. Zollers:

We acknowledge receipt of your submission dated November 01, 2011, for the establishment of an INAD for the use of CP-424,391 in dogs species pursuant to the Federal Food, Drug, and Cosmetic Act, [section 512(j)] and 21 CFR part 511.

Your submission has been assigned **INAD number 012-103** and has been forwarded to the proper reviewer for consideration. Please refer to this number when submitting any future correspondence pertaining to the use of the aforementioned drug.

This letter does not authorize the use of edible products derived from treated food producing animals. If the intended use is in food producing animals, edible products of investigational animals may be used for food only with prior authorization granted by the U.S. Food and Drug Administration.

Sincerely,

Shahin Ahdoot
Records Technician I
Center for Veterinary Medicine
HFV-199

EXHIBIT 11

PROOF OF CONCEPT CLINICAL FIELD STUDY TO EVALUATE THE EFFECTIVENESS OF *AT-002* ON APPETITE IN DOGS

SPONSOR STUDY NUMBER: AT002-CCL-12-001

SPONSOR:

ARATANA THERAPEUTICS, INC.
THE HEARTLAND HOUSE
1901 OLATHE BLVD
KANSAS CITY, KS 66103

VERSION/VERSION DATE: FINAL/20FEB2014

SIGNATURES

ARATANA THERAPEUTICS, INC.

20-Feb-14

Bill Zollers, PhD — Date (DD-MMM-YY)
Vice President – Drug Development

20 FEB 14

Ernst Heinen, DVM, PhD — Date (DD-MMM-YY)
Head of Drug Evaluation and Development

ALCHERABIO, LLC

20 Feb 14

Georgiana Syby, MPH — Date (DD-MMM-YY)
Senior Project Manager

20 Feb 2014

Victoria Lewis, DVM, RPh — Date (DD-MMM-YY)
Director, Research and Development

ghrelin-like activity of *AT-002*) would result in increased body weight and improved quality of life.

Study Schedule

Key Study Dates

First study site trained: 13Aug12

Last study site closed: 8May13

Study completion (final report signature): Final signature date on page 2 of the final study report is the Study Completion date.

Schedule of Monitoring Visits

Table 1: Schedule of Monitoring Visits

PROOF OF CONCEPT CLINICAL FIELD STUDY TO EVALUATE THE EFFECTIVENESS OF *AT-002* ON APPETITE IN DOGS

SPONSOR STUDY NUMBER: AT002-CCL-12-001

SPONSOR: ARATANA THERAPEUTICS INC
THE HEARTLAND HOUSE
1901 OLATHE BLVD
KANSAS CITY, KS 66103

VERSION / VERSION DATE: FINAL/02AUG2012

Protocol Approval Signatures

Sponsor Representative:
Bill Zollers, PhD, Vice President – Drug Development

Bill Zollers
Signature

03 Aug 2012
Date

Monitor/Study Coordinator:
Georgiana Syby, MPH, Senior Clinical Research Coordinator
AlcheraBio – Contract Research Organization

Georgiana Syby
Signature

06 Aug 12
Date

EXHIBIT 12

Xenometrics
Experience | Rapid Turnaround | Flexibility

Final Protocol

AT-002 Dose Titration Study in Adult Beagle Dogs

Xenometrics, LLC Study No.: 10873

Aratana Study Reference No.: AT-002-CCL-13-002

Prepared For:
Aratana Therapeutics
Kansas City, Kansas

Performing Laboratory:
Xenometrics, LLC
Stilwell, Kansas

PROTOCOL ACCEPTANCE

On Behalf of Aratana Therapeutics:

Bill Zollers, Ph.D.
Vice President of Drug Development
Aratana Therapeutics

24 Apr 13
Date

On Behalf of Xenometrics, LLC:

Ryan Losson, B.S.
Study Director
Xenometrics, LLC

29 Apr 13
Date

Sandra D. Love, Ph.D.
Management
Xenometrics, LLC

29 Apr 13
Date

EXHIBIT 13

Xenometrics
Experience | Rapid Turnaround | Flexibility

Final Report

AT-002 Dose Titration Study in Adult Beagle Dogs

Xenometrics, LLC Study No.: 10873

Aratana Study Reference No.: AT-002-CCL-13-002

Prepared For:
Aratana Therapeutics
Kansas City, Kansas

Performing Laboratory:
Xenometrics, LLC
Stilwell, Kansas

REPORT APPROVAL

Ryan Losson, B.S.
Study Director
Xenometrics, LLC

01 Aug 13
Date

Sandra D. Love, Ph.D.
Management
Xenometrics, LLC

01 Aug 13
Date

2. STUDY IDENTIFICATION

2.1. Title

AT-002 Dose Titration Study in Adult Beagle Dogs

2.2. Participating Personnel

Study Sponsor:	Aratana Therapeutics (Aratana) 1901 Olathe Blvd. Kansas City, KS 66103
Sponsor Representative:	Bill Zollers, Ph.D. Vice President of Drug Development Aratana Ph.: (913) 951-2125 E-mail: bzollers@aratana.com
Test Facility:	Xenometrics LLC (Xenometrics) 17745 Metcalf Ave. Stilwell, KS 66085
Study Director:	Ryan Losson, B.S. Scientist Xenometrics Ph.: (913) 850-5007 Fax: (913) 850-5101 E-mail: rlosson@xenometricsllc.com
Test Facility Management:	Sandra Love, Ph.D. Director, Pharmacology Xenometrics Ph.: (913) 850-5003 Fax: (913) 850-5101 E-mail: slove@xenometricsllc.com

2.3. Study Schedule

In-life Start (feeding start):	April 29, 2013
In-Life Start (first dose):	May 9, 2013
In-Life Completion:	May 16, 2013

3. OBJECTIVE

To determine the dose of AT-002 in laboratory dogs that provides the best effectiveness in terms of food consumption and weight gain over a 7 day period.

EXHIBIT 14

PIVOTAL CLINICAL FIELD STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF AT-002 ON STIMULATION OF APPETITE IN DOGS

Protocol Number AT002-CCL-13-003

AUGUST 24, 2015

SPONSOR: ARATANA THERAPEUTICS, INC.
1901 OLATHE BLVD
KANSAS CITY, KS 66103

SIGNATURES

Aratana Therapeutics, Inc.

Bill Zollers, PhD
Vice President – Drug Development

08/25/2015
Date

Ernst Heinen, DVM, PhD
Chief Development Officer

08/25/2015
Date

AlcheraBio, LLC

Georgiana Syby, MPH
Senior Project Manager

08/25/2015
Date

Johnny Jacobsen, DVM, MSc
CRO Management

08/25/2015
Date

a meeting between CVM and Aratana on September 26, 2014, CVM further clarified this requirement and stated: "Each site should have at least 4 evaluable cases (2 placebo and 2 test article). Any site with less than 4 cases should be excluded from the effectiveness evaluation, however these cases should be included in the safety analyses." This clarification was captured in protocol amendment 2 explained in Section 19.1 below.

7.7 Masking Procedures

AT-002 (IVP) and placebo (CP) were matched with regard to liquid appearance and bottle size and shape. The Investigator, Examining Veterinarian, Sponsor, Statistician and other personnel involved in the study were masked to treatment group (IVP or CP) during the study. The blinding was broken after study completion, on June 26, 2015. The Owners were also masked to treatment group (IVP or CP). The Dispensers and AlcheraBio monitors were not masked to treatment code (A, B, C) but were masked to treatment group (IVP or CP).

Prior to November 6, 2014, Dispensers may have acted as a data recorder for the Investigator or Examining Veterinarian. On occasions when this occurred, the Dispenser was not involved in any clinical evaluations or observations. Instead, the Dispenser simply recorded data dictated by the veterinarian. On November 6, 2014, the Dispenser access to Prelude was limited within the EDCS to certain data forms. Beginning on November 7, 2014, the Dispenser could access only the following forms within the EDCS: IVP/CP Received, IVP/CP Dispensing, IVP/CP Reconciliation, Day 0/Day 3 Lab Tests, Dose Calculations, Daily Food Record and Owner Observations. Allowing the Dispenser to participate in data recording helped ensure that data was entered into the EDCS contemporaneously. This did not impact or compromise the study data as the Dispenser only recorded information provided by the Investigator/Examining Veterinarian and the Dispenser was always blinded to treatment group (IVP or CP). A NTF was documented in the EDCS for each site where the Dispenser acted as a data recorder.

8 Study Schedule

8.1 Key Dates

Study Initiation (first site trained)	January 2014
Study Completion (final site closed out)	June 2015
Final Study Report	August 2015

8.2 Key Study Events and Monitoring Visits

Screening/Qualification

- A dog presented at a participating veterinary clinic that was inappetent or had a decreased food intake for at least 2 days could be evaluated for enrollment in the study. It was intended that Day 0 (first dose) be the same day as Screening/Qualification.
- An Owner consent form was signed prior to any study-specific activities taking place.
- A physical examination and preliminary laboratory testing at the veterinary clinic laboratory (at the discretion of the veterinarian) were completed to rule out dogs with severe medical conditions that would preclude enrollment. Preliminary laboratory testing (if completed) was conducted prior to enrollment and was considered part of the medical history.

PIVOTAL CLINICAL FIELD STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF *AT-002* ON STIMULATION OF APPETITE IN DOGS

SPONSOR STUDY NUMBER: AT002-CCL-13-003

SPONSOR: ARATANA THERAPEUTICS, INC.
THE HEARTLAND HOUSE
1901 OLATHE BLVD
KANSAS CITY, KS 66103

VERSION / VERSION DATE: 27DEC13

Protocol Approval Signatures

Sponsor Representative:
Bill Zollers, PhD, Vice President – Drug Development
Aratana Therapeutics, Inc.

Signature 27 Dec 13 Date

Monitor/Study Coordinator:
Georgiana Syby, MPH, Senior Project Manager
AlcheraBio – Contract Research Organization

Signature 02Jan 14 Date

EXHIBIT 15

FINAL PROTOCOL

Study Title:
AT-002: Pharmacokinetic Comparison of Two Formulations in a Cross-Over Design in Beagle Dogs for Two Dose Levels

Study Number: **031599**

Aratana Reference Number: AT002-CPK-14-007

Testing Facility:
Ricerca Biosciences, LLC
Drug Safety and Metabolism
7528 Auburn Road
Concord OH 44077

Approval for Study Initiation

Sponsor Representative

Bill Zollers Date: 03 Jan 14

Bill Zollers, Ph.D.
Aratana Therapeutics. Inc

Study Director

Roger Hawks Date: 3-January-2014

Roger Hawks, Ph.D., DABT
Ricerca Biosciences, LLC

Testing Facility Management

Nicole Stanard Date: 3 JAN 2014

Drug Safety and Metabolism
Ricerca Biosciences, LLC

EXHIBIT 16

REPORT

Study Title
AT-002: Four-Day Repeat Dose Food Consumption Study in Beagle Dogs

Study Number: **031805**
Sponsor Project Number: **AT002-CCL-14-004**

Study Completed:
06-Aug-2014

Author:
Roger Hawks, Ph.D., DABT

Testing Facility:
Ricerca Biosciences, LLC
Drug Safety and Metabolism
7528 Auburn Road
Concord OH 44077

EXHIBIT 17

REPORT

Study Title
AT-002: Pharmacokinetic Comparison of Two Formulations in a Cross-Over Design in Beagle Dogs for Two Dose Levels

Study Number: **031599**
Sponsor Project Number: **AT002-CPK-14-007**

Study Completed:
14-Aug-2014

Author:
Roger Hawks, Ph.D., DABT

Testing Facility:
Ricerca Biosciences, LLC
Drug Safety and Metabolism
7528 Auburn Road
Concord OH 44077

Signatures

Study Title:	AT-002: Pharmacokinetic Comparison of Two Formulations in a Cross-Over Design in Beagle Dogs for Two Dose Levels.
Document Number:	031599-1
Testing Facility:	Ricerca Biosciences, LLC Drug Safety and Metabolism 7528 Auburn Road Concord OH 44077

Study Director

Roger Hawks Date: 14-August-2014

Roger Hawks, Ph.D., DABT
Ricerca Biosciences, LLC

Testing Facility Management

Paul R Dickson III Date: 8/14/14

Drug Safety and Metabolism
Ricerca Biosciences, LLC

Bioanalytical Analysis	Ann Fu, M.S. KCAS, LLC 12400 Shawnee Mission Parkway Shawnee, KS 66216 phone: 913-248-3050 email: Yu-Hui.fu@kcasbio.com
Pharmacokinetic Analysis	Robert H. McClanahan, Ph.D. Ricerca Biosciences, LLC phone: 440-357-3086 email: robert.mcclanahan@ricerca.com
Statistical Analysis	Les Freshwater, M.S. BioSTAT Consultants, Inc. 528 West Centre Avenue Portage, MI 49024 phone: 269-329-7976 email: lesfreshwater@biostat.net

Supervisory Personnel

Technical Director, Toxicology	Ken Draper, Ph.D., DABT
Technical Director, Safety Pharmacology	Michael Stonerook, Ph.D., D.V.M., DABT
Technical Director, Bioanalytical	Jessica LaFlam, B.S.
Attending Veterinarian	Michael Stonerook, Ph.D., D.V.M., DABT

Schedule of Events

Study Initiation	03-Jan-2014
Experimental Start	26-Feb-2014
First Day of Dosing	13-Mar-2014
In-Life Termination	21-Mar-2014
Experimental Completion	10-July-2014

Study Conduct (GLP)

This study was performed according to the protocol, testing facility standard operating procedures, and in accordance with the U.S. Food and Drug Administration (FDA) regulations for Good Laboratory Practices (GLP), Title 21 Code of Federal Regulations Part 58.

EXHIBIT 18

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: 03/22/2016

To: bzollers@aratana.com
Subject: FDA CVM EDSR – User Submission Notification

The Center for Veterinary Medicine, Food and Drug Administration acknowledges the receipt of your eSubmitter submission to the FDA CVM Electronic Submission System. The following information documents the state of your submission. If you have any questions, please submit an email detailing your questions to cvmesubmitter@fda.hhs.gov.

Memo:

Your submission has been accepted and has been forwarded for review.

CVM Received Date:	03/22/2016		
Transmission Identifier:	ci1458663040006.1316873@fdsuv08633_te1		
Submission Identifier:	N-141457-A-0000-OT	Review Division:	HFV-110
Firm Name:	ARATANA THERAPEUTICS INC		
Established Drug Name(s):	CAPROMORELIN		
Submitted Document Type:	NEW ANIMAL DRUG APPLICATION		
Submission Type:	ORIGINAL		
Correspondence Date:	03/21/2016	CVM Due Date:	05/21/2016
Parent Submission:		Reference Submission:	

Notes:

Digital Signature:
Certification signature by CVM ESS, Validity Unknown
Digitally signed by CVM ESS
Date: 2016.03.22 12:17:38 EDT
Reason: I am the author of this document

EXHIBIT 19

10/283,720	PROCESS FOR PREPARING GROWTH HORMONE SECRETAGOGUES	24728A (FP1147-US DIV 1)	03-29-2016::09:38:41

Patent Assignment Abstract of Title

Total Assignments: 2

Application #: 10283720 **Filing Dt:** 10/30/2002 **Patent #:** 6673929 **Issue Dt:** 01/06/2004
PCT #: NONE **Intl Reg #:** **Publication #:** US20030158414 **Pub Dt:** 08/21/2003
Inventors: Frank R. Busch, Charles K. Chiu, Clifford N. Meltz, Ronald J. Post, Peter R. Rose
Title: PROCESS FOR PREPARING GROWTH HORMONE SECRETAGOGUES

Assignment: 1

Reel/Frame: 013476 / 0190 **Received:** 11/14/2002 **Recorded:** 10/30/2002 **Mailed:** 03/13/2003 **Pages:** 4
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:
BUSCH, FRANK R. **Exec Dt:** 02/26/1999
CHIU, CHARLES K. **Exec Dt:** 02/26/1999
MELTZ, CLIFFORD N. **Exec Dt:** 02/26/1999
POST, RONALDS J. **Exec Dt:** 02/26/1999
ROSE, PETER R. **Exec Dt:** 02/26/1999

Assignees:
PFIZER INC.
235 EAST 42ND STREET (150/5)
NEW YORK, NEW YORK 10017-5755
PFIZER PRODUCTS INC.
EASTERN POINT ROAD
BLDG. 260, 1ST FLOOR
GROTON, CONNECTICUT 06340

Correspondent:
PFIZER INC.
GREGG C. BENSON
EASTERN POINT ROAD, MS 8260-1611
GROTON, CT 06340

Assignment: 2

Reel/Frame: 023832 / 0575 **Received:** 01/22/2010 **Recorded:** 01/22/2010 **Mailed:** 01/22/2010 **Pages:** 6
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: PFIZER INC. **Exec Dt:** 01/06/2010

Assignee:
RAQUALIA PHARMA INC.
2, AZA 5-GOCHI,
TAKETOYO-CHO, CHITA-GUN
AICHI-KEN, JAPAN 470-2341

Correspondent:
SCULLY, SCOTT, MURPHY & PRESSER, P.C.
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

Search Results as of: 03/29/2016 09:38:00 AM

Close Window

EXHIBIT 20

EXHIBIT 21

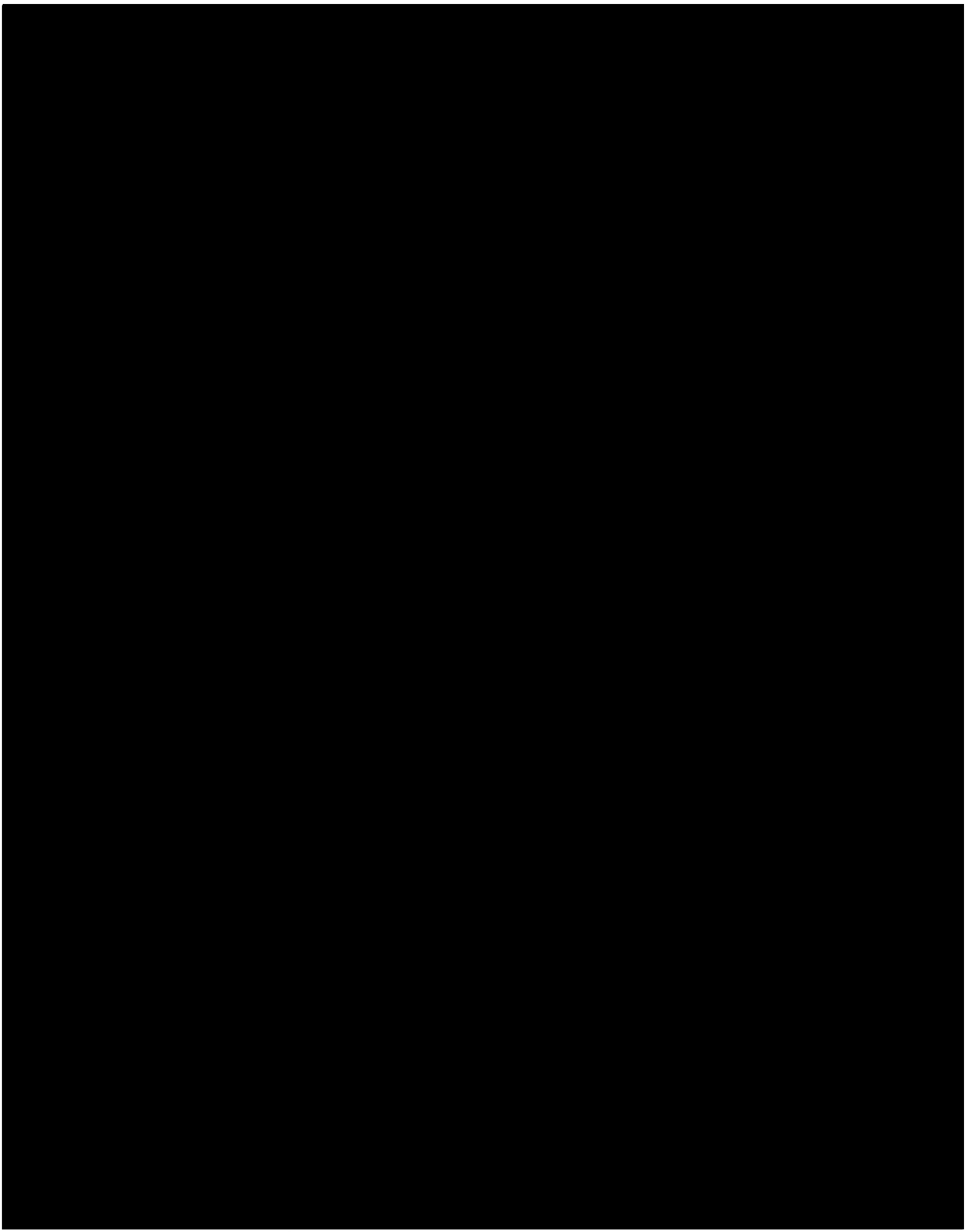


EXHIBIT 23

EXHIBIT 24

EXHIBIT 25

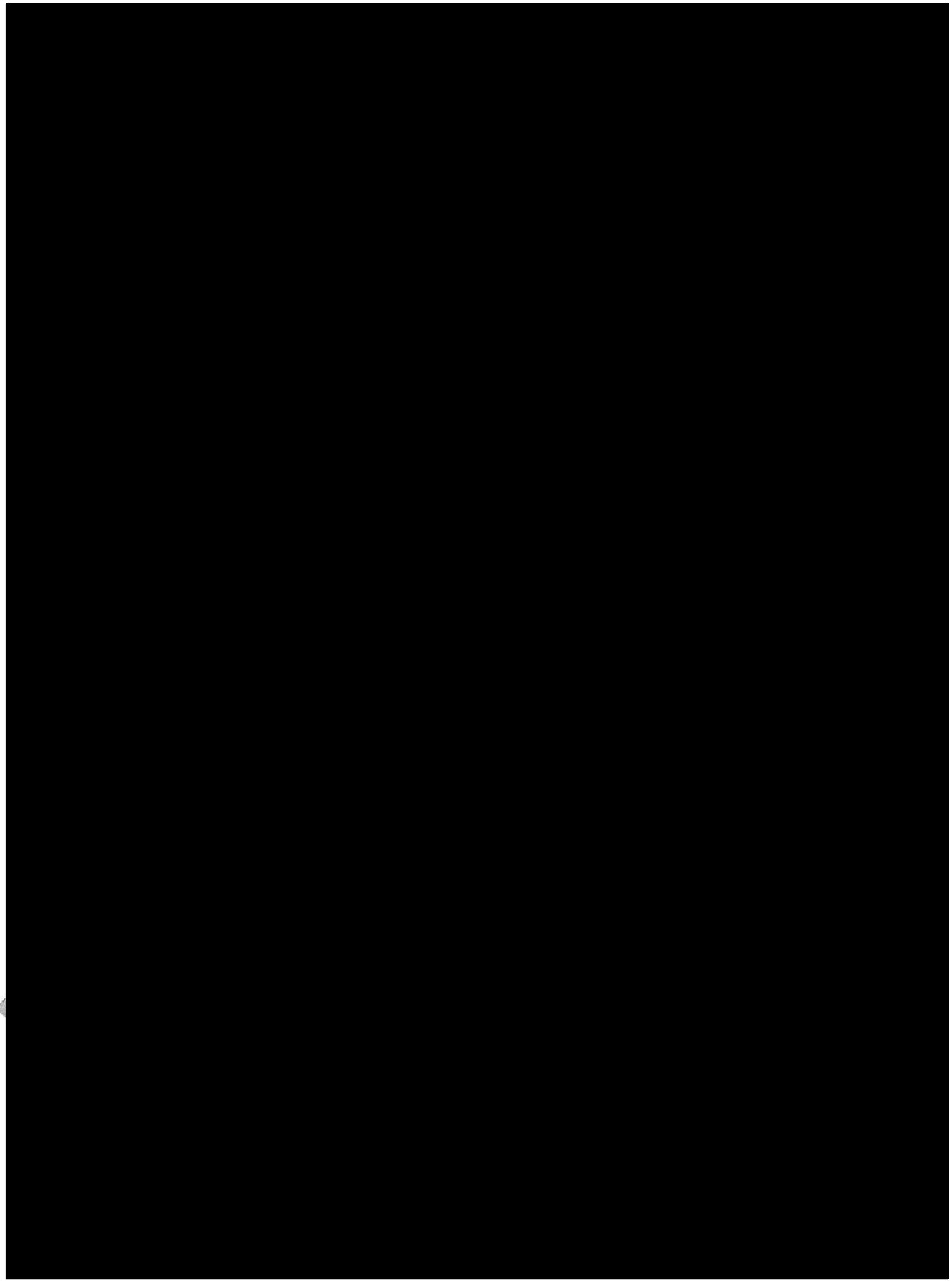


EXHIBIT 27

Veterinary Medicine R&D
Pharmaceuticals Clinical Development
Kalamazoo, MI 49001
United States

Pfizer Animal Health

STUDY NUMBER: 1982R-60-03-302
TITLE: Field efficacy and safety of CP-424,391 in inappetent cats.
PROJECT NAME: CP-424,391
PROJECT CODE: 40AAT0000
INAD Number 11-093

APPROVALS:

Dated: _____ Signed: _____
TBA
Investigator

Dated: 23SEP03 Signed: _____
Mark E. Mazaleski, D.V.M.
Monitor

Dated: 24SEP 2003 Signed: _____
Daniel J. Weigel, Ph.D.
Biometrician, BTQ

Dated: 24SEP2003 Signed: _____
W. Randal Kilgore, D.V.M.
Project Manager, PCD

Dated: 24SEP03 Signed: _____
Robert G. Chesebrough, B.S.
Manager, Regulatory Affairs

Veterinary Medicine Research & Development
Pfizer, Inc.
Kalamazoo, Michigan 49001-0199
United States

Pfizer Animal Health

Final Study Report - Field efficacy and safety of oral CP-424,391 in inappetent cats.

STUDY NUMBER: 1982R-60-03-302
PROJECT NAME: CP-424,391
PROJECT CODE: 4 0 A **A** **T** 0 0 0 0 0

APPROVAL

By signing this report the author affirms that all data were collected in compliance with the Study Protocol (including amendments and deviations), appropriate SOPs and legal requirements. This summary report is an accurate and complete representation of the study activities and results.

Dated: 27 MAR 06 Signed: _____

Mark E. Mazaleski, D.V.M.
Monitor/Author
Pharmaceuticals Clinical Development,
Pfizer Animal Health

Dated: 27 Mar 2006 Signed: _____

W. Randal Kilgore, D.V.M.
Project Manager
Pharmaceuticals Clinical Development
Pfizer Animal Health

14. APPENDIX 2: PROTOCOL 1982R-60-03-302, AMENDMENTS, AND DEVIATIONS.

EXHIBIT 28

EXHIBIT 29

[redacted] Inc. Start-up社（仮称）

(tentative name)

企業価値算定報告書

Report for evaluation of company value

株式会社[redacted]総研
新規産業調査部
2007年12月

[redacted] Institute of Research Ltd.
Reserch department of new industries

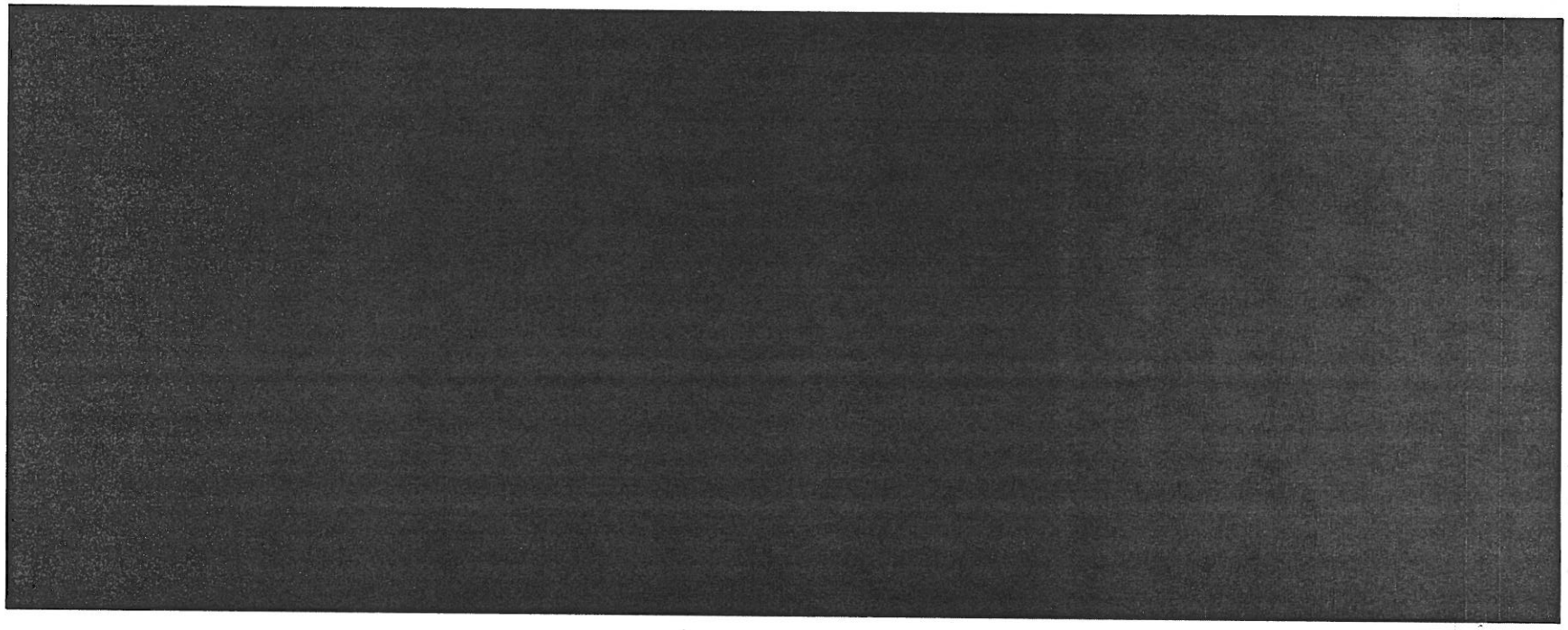
目　次　Table of Contents

Ⅰ．報告書の目的と前提条件 Aim and Precondition

1．報告書の目的 Aim

This report, based on a request from NIF SMBC Ventures K.K., is aimed at evaluating a reference value fo Start-up company to determine an underwritten price when SMBC would receive allocation of new shares to a third party from Pfizer Inc. Accordingly, this report is not used except for above porpose.

本報告書は、エヌ・アイ・エフSMBCベンチャーズ株式会社（以下、「貴社」といいます）からの依頼に基づき、貴社がPfizer Inc. Start-up社（仮称）（以下、「Start-up社」、もしくは「評価対象会社」といいます）の第三者割当増資を引き受けるにあたっての引受価額決定に資する参考価額を算定することを目的としています。
したがいまして、本報告書は上記目的以外の使用に資するものではありません。



Ⅴ．収支予想 Prediction for income and outgo

[redacted]

① 上市前売上高推計に用いた前提条件 Precondition used for sales amount estimate before launch

Pipeline No.	設定条件/パイプライン番号	[redacted]	3	[redacted]
Mechanism Disease	作用機序		Ghrelin agonist	
Development stage	適用疾患または薬効分類		GERD	
Dev.stage at license out time	現在の開発ステージ		第１相臨床試験終了	Phase 1 completed
License out	ライセンス供与時の開発ステージ		第１相臨床試験終了	Phase 1 completed
Preclinical study start	ライセンス供与		2010年	
Phase 1 start	非臨床試験開始		NA	
Phase 2 start	第１相臨床試験開始		NA	
Phase 3 start	第２相臨床試験開始		2010年	
Application for approval	第３相臨床試験開始		2012年	
Market approval	承認申請		2015年	
Upfront (million yen)	承認取得		2017年	
Milestone 1 (P1. million yen)	アップフロント(百万円)		2,100	
Milestone 2 (P2. million yen)	マイルストーン１(第１相臨床試験開始時、百万円)		0	
Milestone 3 (P3. million yen)	マイルストーン２(第２相臨床試験開始時、百万円)		0	
Milestone 4 (Application, million yen)	マイルストーン３(第３相臨床試験開始時、百万円)		3,000	
Minestone 5 (Approval, million yen)	マイルストーン４(承認申請時、百万円)		1,200	
Deal risk discount (%)	マイルストーン５（承認取得時、百万円）		3,600	
	ディールリスク割引率（%）		50.0%	

[redacted]

② 上市後売上高推計に用いた前提条件 Precondition used for sales amount estimate after launch

	設定条件/パイプライン	[redacted]	3	[redacted]
Mechanism	作用機序		Ghrelin agonist	
Disease	適用疾患または薬効分類		GERD	
Development Stage	現在の開発ステージ		第 1 相臨床試験終了	Phase 1 completed
Dev. stage at license out time	ライセンス供与時の開発ステージ		第 1 相臨床試験終了	Phase 1 completed
Launch year	上市年		2019 年	
Market size (million yen)	市場規模（百万円）		2,424,000	
Market share at peak (%)	ピーク時の市場シェア（%）		10.0%	
Sales amount at peak (million yen)	ピーク時の末端売上高（百万円）		242,400	
Peak year	ピーク到達年		2022 年	
Royalty rate (%)	ロイヤリティ率（%）		17%	
Dev. risk discount (%)	開発リスク割引率（%）		18.0%	
Deal risk discount (%)	ディールリスク割引率（%）		50.0%	

[redacted]

[redacted]

③ 開発コスト推計に用いた前提条件

Precondition used for development cost estimate

設定条件/パイプライン番号	[redacted]	3	[redacted]
作用機序		Ghrelin agonist	
適用疾患または薬効分類		GERD	
現在の開発ステージ		第１相臨床試験終了	Phase 1 completed
ライセンス供与時の開発ステージ		第１相臨床試験終了	Phase 1 completed
非臨床試験開始時期		NA	
非臨床試験終了時期		NA	
第１相臨床試験開始時期		NA	
第１相臨床試験終了時期		NA	
後期第２相臨床試験開始時期		NA	
後期第２相臨床試験終了時期		NA	
ライセンス供与時期		2010年Q2	

Pipeline No.
Mechanism Disease
Development stage
Dev. stage at license out time
Preclinical study start
Preclinical study end
Phase 1 start
Phase 1 end
Phase 2b start
Phase 2b end
License out

[redacted]

EXHIBIT 30

Project Name: capromorelin

Compound Number: CP-424,391

Animal Health

Information Category	Information Category Description	Study Number	Report Name	Contributor	Present Data Location (Both Electronic
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs	[redacted]	[redacted]	[redacted]	
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs				
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in				
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed and neutered beagle dogs				
	To evaluate the effect of CP-424,391-18 on food intake in cats following				
	To evaluate the effect of CP-424,391-18 on food intake in cats following				
	To evaluate the effect of CP-424,391-18 on food intake in cats following				
	To evaluate the effect of CP-424,391-18 on food intake in cats following				
	To evaluate the effects of CP-424,391 as an appetite stimulant in cats				
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in cats followin				
	To evaluate the safety of CP-424,391-18 administered in cats.				
	To evaluate the effects of CP-424,391-18 in cats ndpoints include food intake (6 and 24 hour), body weight and plasma drug exposure.				
	To evaluate the effects of CP-424,391-18 in cat Endpoints include food intake (6 and 24 hour), body weight and plasma drug exposure.				
	To evaluate the effects o and CP-424,391-18 as appetite stimulants in cats respectively.				

Project Name: capromorelin					
Compound Number: CP-424,391					
Animal Health					
Information Category	Information Category Description	Study Number	Report Name	Contributor	Present Data Location (Both Electronic
	To determine the orexigenic effects o [redacted] nd CP-424,391-18 when administered concurrently with chemotherapy in normal adult male and female cats.	[redacted]	[redacted]	[redacted]	
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed/neutered cats following eight daily [redacted]				
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in beagle dogs following [redacted]				
	To evaluate the effects of CP-424,391-18 as an appetite stimulant in spayed/neutered cats following [redacted]				

Electronic Transferred To StartUp	Electronic Transfer Date	Electronic Archived In StartUp	Orininal Transferred To StartUp	Original Transfer Date	Original Archived In StartUP	Transferred, Which Site Owns This	Note	Species	# of animals per group	# of dose groups	Dosages (mg/kg)
								Canine	5	2	
☐	2008/##/##	☐	☐	2008/##/##	☐			Canine	5	2	
☐	2008/##/##	☐	☐	2008/##/##	☐			Canine	5	2	
☐	2008/##/##	☐	☐	2008/##/##	☐			Canine	6	2	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	6	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	6	4	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	6	5	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	6	2	

Electronic Transferred To StartUp	Electronic Transfer Date	Electronic Archived In StartUp	Orininal Transferred To StartUp	Original Transfer Date	Original Archived In StartUP	If NOT Transferred, Which Site Owns This	Note	Species	# of animals per group	# of dose groups	Dosages (mg/kg)
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	6	4	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	6	2	
☐	2008/##/##	☐	☐	2008/##/##	☐			Canine	4	1	
☐	2008/##/##	☐	☐	2008/##/##	☐			Feline	5	4	

Dosage Form	Final Report Completed?
[redacted]	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes

Dosage Form	Final Report Completed?
[redacted]	Yes
[redacted]	Yes
[redacted]	Yes
[redacted]	Yes

EXHIBIT 31

[redacted]

差出人: [redacted]
送信日時: 2008年3月11日火曜日 23:09
宛先: [redacted]
件名: RE: Draft Summary of level 2 information for capromorelin
添付ファイル: Inventory List Template(Non clinial clinical) ver 03 10 08 .xls

[redacted]

Attached is the latest version of the level 2 information with capromorelin that was updated with the Pharmacology template filled in to the best of our knowledge at this time. Please note that many who worked in Discovery at the time have left the company and many of the reports were not written but discovery has completed the template with available information. Also, the collaborator list has been completed with the clinical investigators and collaborators used by the discovery team. With regard to CMC, I also note that much of this was missing and I am having the Pharm Sci representative complete a more thorough investigation to provide additional information. The project was transferred from AA to Sandwich last year (August) and many have left the company that worked on the Pharm Sci project from AA. I hope to have this additional information this week.

For the questions raised in the excel spreadsheet by the swat team, I will answer these and get them back to you as soon as possible. For the toxicology questions, these have been answered this morning and I fixed a typo in the original spreadsheet that listed the in vivo cytogenetic study (mouse micronucleus) erroneously as an in vitro study.

Regards,

[redacted]

From: [redacted]
Sent: Tuesday, March 11, 2008 2:17 AM
To: [redacted]
Subject: RE: Draft Summary of level 2 information for capromorelin
Importance: High

Hi [redacted]

Nagoya Program Transfer team SWAT reviewed the draft inventory lists for capromorelin that you provided on March 4.
Please check our comments and questions in the attached file. We hope you or your team members to answer our questions and to provide additional information. Especially, we may need additional work in CMC part. If necessary, we are pleased to have a telecom regarding CMC part.

Thank you very much for your support.

With best regards,

[redacted]

From: [redacted]
Sent: Tuesday, March 04, 2008 5:08 PM
To: [redacted]
Subject: RE: Draft Summary of level 2 information for capromorelin

[redacted]

Thank you for sending the 1st draft of the inventory list. I forwarded the files to my team members for their review. I will compile their questions and will send it to you in this week.

I have one additional question. Based on the information in the inventory list, I actually confirmed that several studies have been conducted in Animal Health. Then, I would like to know the project status of capromorelin for animal health. Is it ongoing or terminated? If terminated, what is the reason?
I would appreciate if you introduce me someone who knows the program in AH. Then I could contact directly.

Once again, thank you very much for your support.

Regards,
[redacted]

From: [redacted]
Sent: Tuesday, March 04, 2008 6:13 AM
To: [redacted]
Subject: Draft Summary of level 2 information for capromorelin

[redacted]

Attached are the templates with level 2 information for capromorelin. The information has been compiled for most tabs in the template. I am still awaiting information on the pharmacology and list of collaborators that I expect within the next few days. This information was requested a few weeks ago, but due to other commitments will be provided this week. I apologize for the delay in getting this information to you. I will update the template as soon as the new information is available.

For your second request for amount of GMP bulk inventory for capromorelin, this request was sent to the appropriate Pharm Sci colleague this morning and I expect to hear back in the next day or two.

Thank you and regards,

[redacted]

From: [redacted]

Sent: Monday, March 03, 2008 2:24 AM

To: [redacted]

Subject: Bulk inventory for Nagoya

Dea[redacted]

As I asked each of you separately, we hope to receive the inventory list with the Level 2 information. One of the requested items in the list is the amount of bulk material.
Could you or your PharmSci colleague please provide the GMP bulk inventory (API and DP) and their expire dates (retest dates) as soon as possible? I need to communicate with CRO who should handle such GMP bulk for Nagoya Start-up.
In the attached file, I summarized the GMP bulk information I have currently. Please check it and provide the latest and relevant information.

Thank you very much for your support.

Program / Person

[redacted]

Capromorelin:[redacted]

[redacted]

With best regards,

[redacted]

****

[redacted]

PGRD Nagoya, Pfizer Japan

Tel [redacted]

[redacted]fizer.com

****

EXHIBIT 32

Final Execution Version

INTELLECTUAL PROPERTY TRANSFER & LICENSE AGREEMENT

BETWEEN

PFIZER INC.

AND

RAQUALIA PHARMA INC.

JUNE 30, 2008

2008-06-30 23:07

EXHIBIT 33

From: [redacted]@pfizer.com]
Sent: Wednesday, November 12, 2008 1:17 AM
To: [redacted]
Cc: [redacted]
Subject: Capromorelin patent estate

Dear [redacted]

I am a patent attorney working for Pfizer in Sandwich, UK and I am responsible for patent matters relating to the GI therapeutic area. I was privileged to meet you briefly on a trip to Nagoya a few years ago and hope everything is going well for you.

We are currently conducting a thorough assessment of the value of our patent assets at Pfizer and cutting back or abandoning those patent families which we do not perceive to be of commercial value. It is my responsibility to make such an assessment of our GI patent portfolio. Four such cases (PC9918, PC9291, PC10464 and PC10845) relate to a compound capromorelin (CP-424391) which was in development at Pfizer for the treatment of GERD and which is now part of the collaboration agreement signed by Pfizer and RaQualia. Specifically, Pfizer have agreed to assign these patent cases to RaQualia following the completion of certain toxicological studies if we believe that the commercialisation of the compound can proceed 'without unreasonable risks' (see page 47).

We are, of course, fully committed to carrying out our obligations under the agreement and are currently maintaining the patent families pending the outcome of the toxicity testing. However, we would like to confirm your interest in these patent families since, in my estimation, some of them may not offer any real value to RaQualia and you may not in fact wish to take them on. Furthermore, some of them are filed rather widely and, even for those cases you are still interested in, you may not wish to maintain all countries.

My comments on the cases are as follows:

- The compound patent (PC9291 - WO-1997/24369) expires Dec 2016 worldwide. When capromorelin was in development at Pfizer it was not anticipated to be launched until after this date and I would assume that timelines will have slipped by a further 2-3 years in the meantime. Extension will not be possible in most jurisdictions since a patent must usually be in force at the MA date to be extended. Even if extension is

still possible, regulatory data protection will drive exclusivity. This case is filed very widely at our 'candidate' list encompassing some 170 territories.

- The tartrate salt patent (PC9918 - WO-1998/58948) expires June 2018 and is likely to have expired before commercialisation. Furthermore, our experience suggests that salt patents are generally insufficient to prevent generic competition since they can be designed around in most jurisdictions. This case is filed at our 'candidate secondary' list encompassing some 45 territories.
- The synthetic process patent (PC10464 - EP-1031575) expires Feb 2020 and is likely to expire round about commercialisation. Our experience is that process patents can almost always be designed around by choosing a different synthetic route such as the one described in the compound patent. This case is filed at our 'candidate secondary' list encompassing some 45 territories.
- The use patent (PC10845 - EP-1159964) expires May 2021 - this might be worth keeping for the time being since it could be extended in major markets to May 2026 and may offer, in a few countries, meaningful protection extending beyond regulatory data exclusivity. This case is filed at our 'limited' list encompassing 9 countries.

I would be grateful if you would consult with your colleagues and let me know if RaQualia would be agreeable to dropping or cutting back any of these patent families.

Many thanks for your help

[redacted]

[redacted]
European Patent Attorney

Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]@pfizer.com

Pfizer Limited is registered in England under No. 526209 with its registered office at Ramsgate Road, Sandwich, Kent CT13 9NJ

EXHIBIT 34

[redacted]

差出人: [redacted]
送信日時: 2008年11月19日水曜日 21:51
宛先: [redacted]
CC: [redacted]
件名: RE: Capromorelin patent estate

Dear [redacted]

I hope you are doing well.
We/RaQualia would like to maintain three patents (PC9291, PC9918, PC10464) with limited [redacted] countries (US, [redacted] On the use patent (PC10845), we would like to keep it with all [redacted] countries in your 'limited' list.

Thank you for your kind consideration in advance.

Cheers,

[redacted]

[redacted]
RaQualia Pharma Inc.
5-2 Taketoyo, Aichi 470-2341, Japan
Tel: [redacted]
Fax: [redacted]
e-mail: [redacted]@raqualia.com

From: [redacted]
Sent: Tuesday, November 18, 2008 4:40 PM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin patent estate

Dear [redacted]

We discussed this matter within our IP team and R&D management, and we agree with your proposal to cut back on the coverage.

[redacted] will communicate the countries we would like to maintain.

regards,

[redacted]

From: [redacted]
Sent: Wednesday, November 12, 2008 8:58 PM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin patent estate

Dear [redacted]

Thank you very much for your note.

I have asked our IP leader [redacted] to analyze the situation along with our IP legal support.

We will get back to you with our thoughts very soon.

regards,

[redacted]

EXHIBIT 35

[redacted]

差出人: [redacted]
送信日時: 2008年12月12日金曜日 19:42
宛先: [redacted]
CC: [redacted]@pfizer.com'
件名: RE: [redacted] Portfolio Review

[redacted]

Thank you for your information of [redacted] portfolio review.

[redacted]

In addition, Capromorelin case (PC9918, PC9291, PC10464, PC10845), we would like to start the assignment procedure from Pfizer to RaQualia as soon as possible.

Could you please set up the IP transfer committee meeting on the agenda of [redacted] 2. assignment of Capromorelin patents? Thank you in advance for your kind cooperation.

Have a good weekend, please.

[redacted]

[redacted]
RaQualia Pharma Inc.
[redacted]
[redacted]@raqualia.com

From: [redacted]@pfizer.com]
Sent: Thursday, December 11, 2008 11:24 AM
To: [redacted]
[redacted]
Subject: RE: [redacted] Portfolio Review

Dear [redacted]

I received update of the portfolio review from the prosecution attorney. [redacted]

Best regards,
[redacted]

From: [redacted]@raqualia.com]
Sent: Friday, December 05, 2008 5:54 PM
To [redacted]
Cc: [redacted]
Subject: RE: [redacted] Portfolio Review

[redacted]

This issue is under consideration in RaQualia. We will respond to this next week. Your patience has been very much appreciated.

Best regards,

[redacted]

From: [redacted]@pfizer.com]
Sent: Thursday, December 04, 2008 9:18 AM
To [redacted]
Cc: [redacted]
Subject: RE: [redacted] Portfolio Review

[redacted]

We would like to finalize the portfolio review ASAP. I appreciate your immediate reply on this matter.

Kind regards,
[redacted]

From: [redacted]@raqualia.com]
Sent: Tuesday, November 25, 2008 6:10 PM
To: [redacted]
Subject: RE: [redacted] Portfolio Review

[redacted]

Thank you for your comments. We will take it under advisement in RaQualia. I will inform you of our reply soon.
Best regards,

[redacted]

[redacted]
RaQualia Pharma Inc.
[redacted]
[redacted]@raqualia.com

From: [redacted]@pfizer.com]
Sent: Tuesday, November 25, 2008 10:45 AM
To: [redacted]
Subject: [redacted] Protfolio Review

To RaQualia
[redacted]

We are reviewing the portfolio of [redacted]

Please confirm these cases and inform me whether the abandonment is acceptable or not.
If you have any questions, please let me know.

Best regards,
[redacted]

[redacted]
Pfizer Japan Inc.
[redacted]
[redacted]@pfizer.com

EXHIBIT 36

STUDY PROTOCOL

HUMAN LYMPHOCYTE ASSAY OF CP-424391M22

STUDY NUMBER: 09GR125

RQA Audit Inspection: [X] Required [ ] Not Required

Final Report: [X] Yes [ ] No

June 2009
Pfizer Global Research & Development
Safety Sciences
Genetic Toxicology
Groton, CT USA

EXHIBIT 37

Inventory list for CP-424391

	Category	Compound ID	Pfizer Lot ID/Vendor Lot	Quantity	Pfizer Storage Location	Retest Date	RaQualia Receiving Date
GMP	API	CP-424391-18	E010003309 (AA0000266)	[redacted]	[redacted]	21-Dec-06	
		CP-424391-18	E010003570 (AA0000266)			30-Jun-2007	
	CP-424,391-18 [redacted]	D0401328	07-054047/CA-0760307			30-Apr-2009	
	CP-424,391-18 [redacted]	D0401328	07-054047/CA-0760307			30-Apr-2009	
	CP-424,391-18 [redacted]	D0602987	07-055327/ CA-0850307			Booked in 30-May-2007	
	CP-424,391-18 [redacted]	D0703350	07-056669 / FP-07-031			30-Apr-2009	
	CP-424,391-18 [redacted]	D0703350	07-056669 / FP-07-031			30-Apr-2009	
	CP-424,391-18 [redacted]	D0703350	07-056669 / FP-07-031			30-Apr-2009	
	Placebo for CP-424,391-18 [redacted]	D0703429	07-056671 / FP-07-030			30-Apr-2012	
	Placebo for CP-424,391-18 [redacted]	D0703429	07-056671 / FP-07-030			30-Apr-2012	
	Capromorel Tartrate [redacted]	G01191AB	03-001740 / ED-G-056-200			Booked in May-2003	

Capromorel Tartrate [redacted]	G01191AB	03-001741 / ED-G-369-X00	[redacted]	Booked in May-2003	
Capromorel Tartrate [redacted]	G01191AB	03-002749 / ED-G-369-X00		30-Apr-2004	
CP-424,391-18 [redacted]	G01192AA	03-001183 / ED-G-057-200		Booked in Apr-03	
CP-424,391-18 [redacted]	G01192AA	03-001192 / ED-G-370-X00		Booked in Apr-03	
CP-424,391-18 [redacted]	G01192AA	03-001196 / ED-G-221-599		Booked in Apr-03	
CP-424,391-18 [redacted]	G01192AA	03-002747 / ED-G-370-X00		30-Apr-2004	
Placebo for Capromorel [redacted]	G01193AB	03-001194 / ED-G-365-X00		30-Noc-2005	
Placebo for Capromorel [redacted]	G01193AB	03-002745 / ED-G-365-X00		1-Nov-2005	
Placebo for CP-424,391-18 [redacted]	G01194AA	03-001172 / ED-G-366-X00		30-Nov-2005	
Placebo for CP-424,391-18 [redacted]	G01194AA	03-002748 / ED-G-366-X00		1-Nov2005	
Placebo for Capromorel [redacted]	G01438AA	03-001099 / ED-G-063-298		31-Dec-2003	
Placebo for CP-424,391-18 [redacted]	G01626AA	03-001222 / ED-G-353-998		31-Oct-2003	

EXHIBIT 38

CONFIDENTIAL

EXPLORATORY BIOLUMINESCENCE AMES ASSAY OF M22 METABOLITE OF CP-424,391

Study Number: 2009-3QB-GN

Pfizer Global Research & Development
Drug Safety Research and Development
Eastern Point Rd
Groton, CT, USA

APPROVAL SIGNATURES

We confirm that this report accurately reflects the interpretation of the data:

Joel Ackerman, MS
Scientist

10/14/09
Date

Joel A. Murray, BS
Scientist
Study Director

10/14/09
Date

Krista Dobo, PhD
Sr. Director

10/14/09
Date

EXHIBIT 39

CONFIDENTIAL

EXPLORATORY IN VITRO MICRONUCLEUS ASSAY OF THE M22 METABOLITE OF CP-424,391

Study Number: CP-424391-2009-3QM-GN

Pfizer Global Research & Development
Drug Safety Research & Development
Eastern Point Rd
Groton, CT, USA

APPROVAL SIGNATURES

I confirm that this report accurately reflects the interpretation of the data:

Andrew Scott, MS
Scientist
Genetic Toxicology

Date: 10/19/09

Approved for Release:

Krista Dobo, PhD
Senior Director
Genetic Toxicology

Date: 10/19/09

EXHIBIT 40

[redacted]

差出人: [redacted]
送信日時: 2009年11月19日木曜日 9:43
宛先: [redacted]
件名: FW: Capromorelin Asset Transfer

ファイザーとのコミュニケーションを転送します。

現在ファイザー側で窓口になっている[redacted]はカプロモレリンの関係者ではないので、RQ からの追加情報リクエストを一つに取りまとめて、彼に送付したいと思います。
皆さんがそれぞれレビューしていただいた結果から足りないものを今日明日中にまとめます。

[redacted]

From: [redacted]
Sent: Thursday, November 19, 2009 9:37 AM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin Asset Transfer

[redacted],

Thank you very much for your update.
I hope you can find the remaining 10 clinical study reports.

The review of the capromorelin information package is in progress in my team, and we found additional missing files in Pharmacology and Regulatory etc. I will inform you and [redacted] the detail of those files in this week.

With best regards,
[redacted]

From: [redacted]@pfizer.com]
Sent: Thursday, November 19, 2009 4:09 AM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin Asset Transfer

[redacted],

I have managed to extract 6 final reports from [redacted] (they were virtual documents that needed to be rendered so they may not have been included in the data dump). The 6 files total about 60MB so I need to work with the IT people to identify the best way to transfer the files to you.

[redacted]

For the remaining 10 Capromorelin reports I could only find draft reports. I am trying to track down someone from the project team that might know where to find the final reports. I'll let you know as soon as I find anything out.

[redacted]

From: [redacted] [mailto:[redacted]@raqualia.com]
Sent: Tuesday, November 17, 2009 9:25 AM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin Asset Transfer

Dear [redacted] and [redacted],

I downloaded the Capromorelin data in [redacted] and transferred them into RaQualia file server today. RaQualia project team started the review of the transferred files and we found the several files are missing. Could you please clarify the reason?

The full clinical study reports for the following 16 clinical studies are not included in the Capromorelin data in [redacted]
- Phase-1 study number; [redacted]
- Phase-2 study number; [redacted]

I confirmed that these reports do not exist in [redacted] Therefore, one of the followings should be the reason.
1) These reports are stored in other Pfizer database.
2) Electronic files are not prepared for these studies and only paper documents are kept somewhere in Pfizer.
3) No study report is prepared for these study.

Thank you for your cooperation.

Best regards,
[redacted]

From: [redacted] [mailto:[redacted]@pfizer.com]
Sent: Friday, November 13, 2009 1:51 AM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin Asset Transfer

[redacted],

The Capromorelin data has been posted on [redacted] in a folder titled "CP-424391 (Capromorelin) Data (20091112)". This will be the last transfer we perform via [redacted] All future transfers will be done via the SharePoint site or external USB drive.

Please confirm when you have successfully downloaded these files.

thanks,
[redacted]

From: [redacted]
Sent: Wednesday, November 04, 2009 8:38 AM
To: [redacted]
Cc: [redacted]
Subject: RE: Capromorelin Asset Transfer

[redacted],

Does this timing meet with your needs? Thanks, dr

NY Office: [redacted]
NL Office: [redacted]
Mobile: [redacted]
Email: [redacted]@pfizer.com

From: [redacted] [mailto:[redacted]@raqualia.com]
Sent: Wednesday, November 04, 2009 2:57 AM
To: [redacted]
Cc: [redacted];
Subject: Capromorelin Asset Transfer

Dear [redacted],

In the Asset Transfer Committee meeting yesterday, we agreed to start the transfer of Capromorelin program (CP-424,391) from Pfizer to RaQualia.
According to the contract between RaQualia and share holders, we need to finish the transfer of key information by end of this year, and I need to report the completion of key transfer to RaQualia Board of Director in the middle of December.
From my experience last year, I think the following schedule could be reasonable to complete it.
Is it possible for you and your team to send a hard disk drive containing file sets for Capromorelin by November 13?
We hope to receive all files related to Capromorelin stored in databases, [redacted] [redacted] and [redacted] and the file format should be [redacted] file system.

Nov. 13; To send a hard disk drive from Pfizer to RaQualia
Nov. 17-18; To receive it at RaQualia and to upload the files into RaQualia IT server
Nov. 19- Dec 11; To review the files by RaQualia team, To have a Q&A communication
Dec. 12 - 18; Communication to the Board
Dec. 18; Completion of transfer

If you have any questions or suggestions, please let me know.

Your kind cooperation would be highly appreciated.

With best regards,
[redacted]

-----Original Appointment-----
From: [redacted]@pfizer.com **On Behalf Of** [redacted]
Sent: Monday, July 13, 2009 9:42 PM
To: [redacted]
Cc: [redacted]
Subject: Updated: RaQualia/Pfizer Asset Transfer Committee
When: 2009年11月3日火曜日 22:30-23:00 (GMT+09:00) 大阪、札幌、東京
Where: Telecon: see below

Dial in
[redacted]
Chairperson: [redacted]
participant passcode: [redacted]

Japan [redacted] [redacted] [redacted]

EXHIBIT 41

報告書

ファイザーからラクオリアへのGhrelin agonistプログラム移管

２００９年１２月１１日

ラクオリア創薬株式会社

Ghrelin agonistプロジェクトチーム

[redacted]

Report

Transfer Ghrelin agonist program from Pfizer to RaQualia

December 11, 2009

RaQualia Pharma Inc.

Ghrelin agonist project team

[redacted]

1. まとめ

- 2008 年 6 月 30 日にファイザーとラクオリアの間で締結された Intellectual property transfer & license agreement の内容に従い、Ghrelin agonist（グレリン・アゴニスト）プログラムおよび開発化合物 Capromorelin（カプロモレリン）に関して、ファイザーよりラクオリアへの知的財産（情報、マテリアル、特許）の移管を 2009 年 10 月より 12 月にかけて実施した。

2. 情報移管

- カプロモレリンの研究・開発を進めるに必要な科学的データおよびレポート、医薬品承認申請時に必要な情報・書類、当局とのやり取りに関しての情報などを移管した。それらの情報は、研究・開発の技術的情報であり、導客候補が導入決定を行う際に必要なものである。
- 移管した技術情報は、各専門分野（臨床、薬事、薬理、毒性、薬物動態、CMC）などの分野に関わる電子ファイルであり、その総計は [redacted] 個であった。移管の確認は、ラクオリアの Ghrelin agonist プロジェクトリーダーがインベントリーリスト（添付資料 1）を作成することにより実施し、移管完了シート（サインオフシート）にサインをすることにより証明した。（添付資料 2）

3. マテリアル移管

- Capromorelin に関係する治験薬の特定およびその保管場所を確認した（添付資料 3）。また研究・開発に用いることを目的として [redacted] 個の化合物をラクオリアに移管した。今後のビジネス上の必要性に応じて治験薬は移管する予定である。

4. 特許移管

- ラクオリアは、ファイザーと協力して、移管すべき特許を特定し、その特許状況を確認した（資料 4）。[redacted]特許事務所を通じて、それぞれの特許および各国の状況に応じて、出願人の変更（出願中の特許について）または名義変更（成立後の特許について）などの準備を順次、計画的に進めている。

1. Summary

- According to "Intellectual property transfer & License agreement" signed between Pfizer and RaQualia dated on June 30th, 2008, Intellectual assets (information, material and IP) of Ghrelin agonist and Capromorelin program had been transfered from Pfizer to RaQualia over the period of October 2009 to December 2009.

2. Information Transfer

- Scientific data, reports required for the development of Capromorelin, regulatory documents and correspondences to the authorities were transferred from Pfizer. These information as technical information are necessary for RaQualia's licensing activity.

- Transferred technical information is electric files related to each area of expertise (clinical, regulatory, pharmacology, toxicology, pharmacokinetics and CMC). Total number was XX files. The confirmation of transfer was completed by Ghrelin agonist project leader by making an inventory list (Attachment 1) followed by executed sigh-off sheet (Attachment 2).

3. Material Transfer

- Completed the confirmation of specifying investigational medical products related to Capromorelin and their storage area. Some of them were transferred to RaQualia in order to use them for further development. The rest are going to be transferred as necessary.

4. IP Transfer

- RaQualia specified IPs and confirmed their IP status in consultation with Pfizer.(Attachment 4) RaQualia is preparing for change of applicant as the domestic IP demands through a patent attorney in a planned way.

資料1　インベントリーリスト

薬理レポート

試験番号・ファイル名	試験タイトル・書類タイトル
DB2_Ghrelin_2006_[redacted]	Evaluation of CP-424,391 and CP-464,709 in GI models
DS_PDM_ExpGI_2006_[redacted]	Acetaminophen conc. in dog plasma [redacted] mg/kg, Oral, Single)
1Dog.xls	イヌの胃排出能測定(CP-424,391 [redacted] mg/kg p.o.)
Ghrelin_Dog.xls	イヌ胃運動・胃排出試験まとめ
Ghrelin_Rat GE.xls	ラット胃排出試験まとめ
060123mtg[redacted].ppt	DB2 monthly meeting 発表資料
DB2MM_[redacted].ppt	DB2 monthly meeting 発表資料
[redacted]_Lab_2006_03.doc	Monthly Report : DB2[redacted] Lab
[redacted]_2006_04.doc	Monthly Report : DB2[redacted] Lab
[redacted]_2006_05.doc	Monthly Report : DB2[redacted] Lab
03-1340[redacted]	METHODS DEVELOPMENT FOR GASTROINTESTINAL TRANSIT IN SPRAGUE-DAWLEY RATS
97-1340[redacted]	CP-424,391-18 EXPLORATORY TOLERATION STUDY IN CYNOMOLGUS MONKEYS
	Cardiovascular evaluation of CP-424,391-18 in conscious primates. Jul 15,2003
	General Pharmacology Summary CP-424,391July 25, 1996
	Growth Hormone Secretagogue: CP424,391 Summay of Pharmacological Properties (Revised) May 8, 1997
	CP 424,391 Pharmacology Summary

薬物動態レポート

試験番号・ファイル名	試験タイトル・書類タイトル
DM1996-424391[redacted]	Assay Validation for CP-424,391 in Rat, Dog and Mouse Plasma
DM1995-424391[redacted]	Pharmacokinetics of CP-424,391 in Female Sprague-Dawley Rats Following a Single Oral or Intravenous Dose of [redacted] mg/kg
DM1995-424391[redacted]	Pharmacokinetics of CP-424,391 in Male and Female Beagle Dogs Following a Single Intravenous or Oral Dose of [redacted] mg/kg in Beagle Dogs
DM1998-424391[redacted]	Systemic Exposure to CP-424,391 in Cynomolgus Monkeys Following a

資料1 Inventory List

Reports for pharmacology

Study No. file name	試Study title / Document title
DB2_Ghrelin_2006_[redacted]	Evaluation of CP-424,391 and CP-464,709 in GI models
DS_PDM_ExpGI_2006_[redacted]	Acetaminophen conc. in dog plasma [redacted] mg/kg, Oral, Single)
1Dog.xls	Gastric emptying dog(CP-424,391 [redacted] mg/kg p.o.)
Ghrelin_Dog.xls	Summary for gastric motility and emptying in dogs
Ghrelin_Rat GE.xls	Summary for gastric motility and emptying in rats
060123mtg[redacted].ppt	DB2 monthly meeting presentation material
DB2MM_[redacted].ppt	DB2 monthly meeting presentation material
[redacted]_Lab_2006_03.doc	Monthly Report : DB2[redacted] Lab
[redacted]_2006_04.doc	Monthly Report : DB2[redacted] Lab
[redacted]_2006_05.doc	Monthly Report : DB2[redacted] Lab
03-1340[redacted]	METHODS DEVELOPMENT FOR GASTROINTESTINAL TRANSIT IN SPRAGUE-DAWLEY RATS
97-1340[redacted]	CP-424,391-18 EXPLORATORY TOLERATION STUDY IN CYNOMOLGUS MONKEYS
	Cardiovascular evaluation of CP-424,391-18 in conscious primates. Jul 15,2003
	General Pharmacology Summary CP-424,391July 25, 1996
	Growth Hormone Secretagogue: CP424,391 Summay of Pharmacological Properties (Revised) May 8, 1997
	CP 424,391 Pharmacology Summary

Reports for pharmacokinetics

Study No. file name	Study title / Document title
DM1996-424391[redacted]	Assay Validation for CP-424,391 in Rat, Dog and Mouse Plasma
DM1995-424391[redacted]	Pharmacokinetics of CP-424,391 in Female Sprague-Dawley Rats Following a Single Oral or Intravenous Dose of [redacted] mg/kg
DM1995-424391[redacted]	Pharmacokinetics of CP-424,391 in Male and Female Beagle Dogs Following a Single Intravenous or Oral Dose of [redacted] mg/kg in Beagle Dogs
DM1998-424391[redacted]	Systemic Exposure to CP-424,391 in Cynomolgus Monkeys Following a

	Single [redacted] mg/kg Intravenous or Oral Dose
DM1996-424391[redacted]	Systemic Exposure to CP-424,391 and the Metabolite CP-420,866 in the Male Sprague-Dawley Rat Following a Single Dose of [redacted] mg/kg of CP-424,391
DM1998-424391[redacted]	Plasma Concentrations of CP-424,391 in the Female Rabbit Following Oral Administration of [redacted] mg/kg Doses
DM1995-424391[redacted]	Pharmacokinetics of CP-424,391 in Male and Female Beagle Dogs Following a Single Intravenous or Oral Dose of [redacted] mg/kg in Beagle Dogs
DM-1998-424391[redacted]	Systemic Exposure to CP-424,391 and the Metabolite, CP-420,866, in Male and Female Mongrel Dogs Following a Single Oral Dose of [redacted] mg/kg
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Male and Female Mongrel Dogs Following a Single [redacted] mg/kg Oral Dose.
DM1998-424391[redacted]	Systemic Exposure to CP-424,391 in Cynomolgus Monkeys Following a Single [redacted] mg/kg Intravenous or Oral Dose
DM1998-424391[redacted]	Systemic Exposure to CP-424,391 in Male Yorkshire Pigs Following a Single [redacted] mg/kg Intravenous Dose or a Single [redacted] mg/kg Oral Dose
DM1998-424391[redacted]	Plasma Concentrations of CP-424,391 Following [redacted] of [redacted] mg/kg in the Diet of Male and Female CD-1 Mice
DM1996-424391[redacted]	Systemic Exposure to CP-424,391 and the Metabolite, CP 420,866, in the CD-1 Mouse Following a Daily Oral Dose of [redacted] mg/kg for [redacted] Consecutive Days
DM1998-424391[redacted]	Plasma Concentrations of CP-424,391 Following [redacted] of [redacted] mg/kg in the Diet of Male and Female Sprague-Dawley Rats
DM2006-424391[redacted]	Multiple-Dose CSF and Plasma Pharmacokinetics of CP-424,391 in Subarachnoid-catheterized Beagle Dogs Following BID Oral Administration at [redacted] mg/kg for [redacted] Days
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Rats Following a Single Oral Dose of [redacted] mg/kg
DM1996-424391[redacted]	Systemic exposure to CP-424,391 and metabolite CP-420,866 in Sprague-Dawley rats following daily oral dose of [redacted] mg/kg of CP-424,391 for [redacted]
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Male and Female Sprague-Dawley Rats Following a Daily [redacted] mg/kg Oral Dose for [redacted]
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Male and Female Beagle Dogs Following an Oral Dose of [redacted] mg/kg

	Single [redacted] mg/kg Intravenous or Oral Dose
DM1996-424391[redacted]	Systemic Exposure to CP-424,391 and the Metabolite CP-420,866 in the Male Sprague-Dawley Rat Following a Single Dose of [redacted] mg/kg of CP-424,391
DM1998-424391[redacted]	Plasma Concentrations of CP-424,391 in the Female Rabbit Following Oral Administration of [redacted] mg/kg Doses
DM1995-424391[redacted]	Pharmacokinetics of CP-424,391 in Male and Female Beagle Dogs Following a Single Intravenous or Oral Dose of [redacted] mg/kg in Beagle Dogs
DM-1998-424391[redacted]	Systemic Exposure to CP-424,391 and the Metabolite, CP-420,866, in Male and Female Mongrel Dogs Following a Single Oral Dose of [redacted] mg/kg
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Male and Female Mongrel Dogs Following a Single [redacted] mg/kg Oral Dose.
DM1998-424391[redacted]	Systemic Exposure to CP-424,391 in Cynomolgus Monkeys Following a Single [redacted] mg/kg Intravenous or Oral Dose
DM1998-424391[redacted]	Systemic Exposure to CP-424,391 in Male Yorkshire Pigs Following a Single [redacted] mg/kg Intravenous Dose or a Single [redacted] mg/kg Oral Dose
DM1998-424391[redacted]	Plasma Concentrations of CP-424,391 Following [redacted] of [redacted] mg/kg in the Diet of Male and Female CD-1 Mice
DM1996-424391[redacted]	Systemic Exposure to CP-424,391 and the Metabolite, CP 420,866, in the CD-1 Mouse Following a Daily Oral Dose of [redacted] mg/kg for [redacted] Consecutive Days
DM1998-424391[redacted]	Plasma Concentrations of CP-424,391 Following [redacted] of [redacted] mg/kg in the Diet of Male and Female Sprague-Dawley Rats
DM2006-424391[redacted]	Multiple-Dose CSF and Plasma Pharmacokinetics of CP-424,391 in Subarachnoid-catheterized Beagle Dogs Following BID Oral Administration at [redacted] mg/kg for [redacted] Days
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Rats Following a Single Oral Dose of [redacted] mg/kg
DM1996-424391[redacted]	Systemic exposure to CP-424,391 and metabolite CP-420,866 in Sprague-Dawley rats following daily oral dose of [redacted] mg/kg of CP-424,391 for [redacted]
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Male and Female Sprague-Dawley Rats Following a Daily [redacted] mg/kg Oral Dose for [redacted]
DM1997-424391[redacted]	Systemic Exposure to CP-424,391 in Male and Female Beagle Dogs Following an Oral Dose of [redacted] mg/kg

DM1996-424391	Systemic exposure to CP-424,391 and the metabolite CP-420,866 in beagle dogs following daily oral doses of [redacted] mg/kg of CP-424,391 for [redacted] days - toxicology study number 96-1340 [redacted]
DM1997-424391	Systemic Exposure to CP-424,391 in Male and Female Beagle Dogs Following a Daily [redacted] mg/kg Oral Dose for [redacted]
DM1997-424391	Systemic Exposure to CP-424,391 in Male and Female Cynomolgus Monkeys Following a Single [redacted] mg/kg Oral Dose
DM1999-424391	CP-424,391-18 Toxicokinetics for Reproductive Study III ? Teratology in Sprague-Dawley Rats
DM1999-424391	CP-424,391 Toxicokinetics for Reproductive Study III - Teratology in New Zealand White Rabbits
DM1999-424391	Tissue Distribution of CP-424,391 in Long-Evans Rats (Report No. [redacted] CP424391-WBAL)
DM1996-424391	In Vitro Plasma Protein Binding and Red Blood Cell Partitioning of CP-424,391 in Rat, Dog and Man
DM1996-424391	In Vitro Plasma Protein Binding and Red Blood Cell Partitioning of CP-424,391 in Rat, Dog and Man
DM2006-424391	Multiple-Dose CSF and Plasma Pharmacokinetics of CP-424,391 in Subarachnoid-catheterized Beagle Dogs Following BID Oral Administration at [redacted] mg/kg for [redacted]
DM1999-424391	Material Balance, Pharmacokinetics, and Biotransformation of 14C-CP-424,391 in Mice Following Oral Administration
DM1997-424391	Material Balance and Biotransformation of 14C-CP-424,391 in Sprague-Dawley Rats Following Oral Administration
DM1997-424391	Identification of CP-424,391 Metabolites in Dog Bile, Urine and Plasma.
DM1997-424391	Material Balance and Metabolism of CP-424,391 in Beagle Dogs Following Oral Administration of [14C]CP-424,391
DM1997-424391	Material Balance and Metabolism of CP-424,391 in Cynomolgus Monkeys Following Oral Administration of [14C]CP-424,391
DM1999-424391	Material Balance, Pharmacokinetics, and Biotransformation of 14C-CP-424,391 in Mice Following Oral Administration
DM1997-424391	Material Balance and Biotransformation of 14C-CP-424,391 in Sprague-Dawley Rats Following Oral Administration
DM1997-424391	Material Balance and Metabolism of CP-424,391 in Beagle Dogs Following Oral Administration of [14C]CP-424,391
DM1997-424391	Identification of Major Human Hepatic Microsomal P450 Isozymes

DM1996-424391	Systemic exposure to CP-424,391 and the metabolite CP-420,866 in beagle dogs following daily oral doses of [redacted] mg/kg of CP-424,391 for [redacted] days - toxicology study number 96-1340 [redacted]
DM1997-424391	Systemic Exposure to CP-424,391 in Male and Female Beagle Dogs Following a Daily [redacted] mg/kg Oral Dose for [redacted]
DM1997-424391	Systemic Exposure to CP-424,391 in Male and Female Cynomolgus Monkeys Following a Single [redacted] mg/kg Oral Dose
DM1999-424391	CP-424,391-18 Toxicokinetics for Reproductive Study III ? Teratology in Sprague-Dawley Rats
DM1999-424391	CP-424,391 Toxicokinetics for Reproductive Study III - Teratology in New Zealand White Rabbits
DM1999-424391	Tissue Distribution of CP-424,391 in Long-Evans Rats (Report No. [redacted] CP424391-WBAL)
DM1996-424391	In Vitro Plasma Protein Binding and Red Blood Cell Partitioning of CP-424,391 in Rat, Dog and Man
DM1996-424391	In Vitro Plasma Protein Binding and Red Blood Cell Partitioning of CP-424,391 in Rat, Dog and Man
DM2006-424391	Multiple-Dose CSF and Plasma Pharmacokinetics of CP-424,391 in Subarachnoid-catheterized Beagle Dogs Following BID Oral Administration at [redacted] mg/kg for [redacted]
DM1999-424391	Material Balance, Pharmacokinetics, and Biotransformation of 14C-CP-424,391 in Mice Following Oral Administration
DM1997-424391	Material Balance and Biotransformation of 14C-CP-424,391 in Sprague-Dawley Rats Following Oral Administration
DM1997-424391	Identification of CP-424,391 Metabolites in Dog Bile, Urine and Plasma.
DM1997-424391	Material Balance and Metabolism of CP-424,391 in Beagle Dogs Following Oral Administration of [14C]CP-424,391
DM1997-424391	Material Balance and Metabolism of CP-424,391 in Cynomolgus Monkeys Following Oral Administration of [14C]CP-424,391
DM1999-424391	Material Balance, Pharmacokinetics, and Biotransformation of 14C-CP-424,391 in Mice Following Oral Administration
DM1997-424391	Material Balance and Biotransformation of 14C-CP-424,391 in Sprague-Dawley Rats Following Oral Administration
DM1997-424391	Material Balance and Metabolism of CP-424,391 in Beagle Dogs Following Oral Administration of [14C]CP-424,391
DM1997-424391	Identification of Major Human Hepatic Microsomal P450 Isozymes

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	Catalyzing CP-424,391 Metabolism
DM1999-424391	Identification of P450 Isoforms Responsible for the Metabolism of CP-424,391
DM2001-424391	Effect of CP-424,391-18 on Human Drug Metabolizing Enzymes In Vitro
DM1997-424391	Material Balance and Biotransformation of 14C-CP-424,391 in Sprague-Dawley Rats Following Oral Administration
DM1999-424391	An Open Study to Examine the Metabolism and Excretion of 14C-CP-424,391-18 in Healthy Male Volunteers
DM1997-424391	Identification of Metabolites of CP-424,391 in Human Liver Slice Incubation
DM2000-424391	Cytochrome P450 Interaction and Inactivation Studies with CP-424,391 and CP-420,866
DM1999-424391	Summary Report for Interaction of CP-424,391 with Human Liver Cytochromes P450: Results of IC50 Determinations
DM1999-424391	Projection of Human Exposure to Carbon-14 Radioactivity following Oral Administration of 100 uCi [14C]CP-424,391 in Human Research Subjects (Report No. [redacted] CP424391-Dosimetry)

毒性レポート

試験番号・ファイル名	試験タイトル・報告タイトル
98-1340	CP-424,391-18 EXPLORATORY RABBIT TOLERATION STUDY Dose Levels: [redacted] mg/kg/day
96-1340	CP-424,391-18 SINGLE DOSE ORAL AND INTRAVENOUS TOXICITY STUDIES IN MICE AND RATS
97-1340	CP-424,391-18 SINGLE DOSE ORAL TOXICITY STUDY IN RATS
96-1340	CP-424,391-18 Exploratory Dose Escalation Study in Beagle Dogs Dose Levels: [redacted] mg/kg/day
990	CP-424,391-18 [redacted] ORAL RANGE-FINDING TOXICITY STUDY IN CD1 MICE Dose levels : [redacted] mg/kg
96-1340	CP-424,391-18 [redacted] ORAL TOXICITY STUDY IN SPRAGUE-DAWLEY RATS Dose Levels: [redacted] mg/kg/day
96-1340	CP-424,391 -18 [redacted] ORAL TOXICITY STUDY IN BEAGLE DOGS Dose Levels: [redacted] mg/kg/day
990	CP-424,391-18 [redacted] ORAL PRECHRONIC TOXICITY STUDY IN CD1 MICE Dose levels: [redacted] mg/kg
96-1340	CP-424,391-18 [redacted] ORAL TOXICITY STUDY IN

	Catalyzing CP-424,391 Metabolism
DM1999-424391	Identification of P450 Isoforms Responsible for the Metabolism of CP-424,391
DM2001-424391	Effect of CP-424,391-18 on Human Drug Metabolizing Enzymes In Vitro
DM1997-424391	Material Balance and Biotransformation of 14C-CP-424,391 in Sprague-Dawley Rats Following Oral Administration
DM1999-424391	An Open Study to Examine the Metabolism and Excretion of 14C-CP-424,391-18 in Healthy Male Volunteers
DM1997-424391	Identification of Metabolites of CP-424,391 in Human Liver Slice Incubation
DM2000-424391	Cytochrome P450 Interaction and Inactivation Studies with CP-424,391 and CP-420,866
DM1999-424391	Summary Report for Interaction of CP-424,391 with Human Liver Cytochromes P450: Results of IC50 Determinations
DM1999-424391	Projection of Human Exposure to Carbon-14 Radioactivity following Oral Administration of 100 uCi [14C]CP-424,391 in Human Research Subjects (Report No. [redacted] CP424391-Dosimetry)

Reports for toxicology

Study No. file name	Study title / Document title
98-1340	CP-424,391-18 EXPLORATORY RABBIT TOLERATION STUDY Dose Levels: [redacted] mg/kg/day
96-1340	CP-424,391-18 SINGLE DOSE ORAL AND INTRAVENOUS TOXICITY STUDIES IN MICE AND RATS
97-1340	CP-424,391-18 SINGLE DOSE ORAL TOXICITY STUDY IN RATS
96-1340	CP-424,391-18 Exploratory Dose Escalation Study in Beagle Dogs Dose Levels: [redacted] mg/kg/day
990	CP-424,391-18 [redacted] ORAL RANGE-FINDING TOXICITY STUDY IN CD1 MICE Dose levels [redacted] mg/kg
96-1340	CP-424,391-18 [redacted] ORAL TOXICITY STUDY IN SPRAGUE-DAWLEY RATS Dose Levels: [redacted] mg/kg/day
96-1340	CP-424,391 -18 [redacted] ORAL TOXICITY STUDY IN BEAGLE DOGS Dose Levels: [redacted] mg/kg/day
990	CP-424,391-18 [redacted] ORAL PRECHRONIC TOXICITY STUDY IN CD1 MICE Dose levels: [redacted] mg/kg
96-1340	CP-424,391-18 [redacted] ORAL TOXICITY STUDY IN

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	SPRAGUE-DAWLEY RATS Dose Levels: [redacted] mg/kg/day
96-1340[redacted]	CP-424,391-18[redacted] ORAL TOXICITY STUDY IN BEAGLE DOGS Dose Levels: [redacted] mg/kg/day
95-1340[redacted]	CP-424,391-18 REVERSE MUTATION TEST IN SALMONELLA: SPIRAL MODIFICATION
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 MICROBIAL REVERSE MUTATION ASSAYS
96-1340[redacted]	CP-424,391 PROCESS INTERMEDIATES REVERSE MUTATION TEST IN SALMONELLA: SPIRAL MODIFICATION
2009-3QB[redacted]	EXPLORATORY BIOLUMINESCENCE AMES ASSAY OF M22 METABOLITE OF CP-424,391
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 MAMMALIAN MUTATION ASSAYS
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 IN VITRO CYTOGENETIC ASSAYS (Human Lymphocyte Aberration Assay)
96-1340[redacted]	EXPLORATORY GENETIC TOXICOLOGY REPORT CP-424,391-18 IN VITRO MITOTIC SPINDLE ASSAY
CP-424391-2009[redacted]	EXPLORATORY IN VITRO MICRONUCLEUS ASSAY OF THE M22 METABOLITE OF CP-424,391
09GF[redacted]	HUMAN LYMPHOCYTE ASSAY OF CP-424391M22
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 MOUSE MICRONUCLEUS ASSAY ORAL ROUTE
98-1340[redacted] and A8-1340[redacted]	CP-424,391-18[redacted] WEEK IN-FEED PALATABILITY STUDY IN CD-1 MICE Dose levels: [redacted] mg/kg/day
98-1340[redacted] and A8-1340[redacted]	CP-424,391-18[redacted] WEEK IN-FEED PALATABILITY STUDY IN SPRAGUE-DAWLEY RATS Dose levels: [redacted] mg/kg/day
98-1340[redacted]	CP-424,391-18 RANGE FINDING STUDY IN PREGNANT SPRAGUE-DAWLEY RATS ORAL GAVAGE Dose Levels: [redacted] mg/kg/day
99-1340[redacted]	CP-424,391-18 REPRODUCTIVE STUDY III: TERATOLOGY IN SPRAGUE-DAWLEY RATS ORAL GAVAGE Dose Levels: [redacted] mg/kg/day
98-1340[redacted]	CP-424,391-18 RANGE FINDING STUDY IN PREGNANT NEW ZEALAND WHITE RABBITS Dose Levels: [redacted] mg/kg
99-1340[redacted]	CP-424,391-18 REPRODUCTIVE STUDY III: TERATOLOGY IN NEW

	SPRAGUE-DAWLEY RATS Dose Levels: [redacted] mg/kg/day
96-1340[redacted]	CP-424,391-18[redacted] ORAL TOXICITY STUDY IN BEAGLE DOGS Dose Levels: [redacted] mg/kg/day
95-1340[redacted]	CP-424,391-18 REVERSE MUTATION TEST IN SALMONELLA: SPIRAL MODIFICATION
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 MICROBIAL REVERSE MUTATION ASSAYS
96-1340[redacted]	CP-424,391 PROCESS INTERMEDIATES REVERSE MUTATION TEST IN SALMONELLA: SPIRAL MODIFICATION
2009-3QB[redacted]	EXPLORATORY BIOLUMINESCENCE AMES ASSAY OF M22 METABOLITE OF CP-424,391
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 MAMMALIAN MUTATION ASSAYS
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 IN VITRO CYTOGENETIC ASSAYS (Human Lymphocyte Aberration Assay)
96-1340[redacted]	EXPLORATORY GENETIC TOXICOLOGY REPORT CP-424,391-18 IN VITRO MITOTIC SPINDLE ASSAY
CP-424391-2009[redacted]	EXPLORATORY IN VITRO MICRONUCLEUS ASSAY OF THE M22 METABOLITE OF CP-424,391
09GF[redacted]	HUMAN LYMPHOCYTE ASSAY OF CP-424391M22
96-1340[redacted]	GENETIC TOXICOLOGY REPORT CP-424,391-18 MOUSE MICRONUCLEUS ASSAY ORAL ROUTE
98-1340[redacted] and A8-1340[redacted]	CP-424,391-18[redacted] WEEK IN-FEED PALATABILITY STUDY IN CD-1 MICE Dose levels: [redacted] mg/kg/day
98-1340[redacted] and A8-1340[redacted]	CP-424,391-18[redacted] WEEK IN-FEED PALATABILITY STUDY IN SPRAGUE-DAWLEY RATS Dose levels: [redacted] mg/kg/day
98-1340[redacted]	CP-424,391-18 RANGE FINDING STUDY IN PREGNANT SPRAGUE-DAWLEY RATS ORAL GAVAGE Dose Levels: [redacted] mg/kg/day
99-1340[redacted]	CP-424,391-18 REPRODUCTIVE STUDY III: TERATOLOGY IN SPRAGUE-DAWLEY RATS ORAL GAVAGE Dose Levels: [redacted] mg/kg/day
98-1340[redacted]	CP-424,391-18 RANGE FINDING STUDY IN PREGNANT NEW ZEALAND WHITE RABBITS Dose Levels: [redacted] mg/kg
99-1340[redacted]	CP-424,391-18 REPRODUCTIVE STUDY III: TERATOLOGY IN NEW

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	ZEALAND WHITE RABBITS ORAL GAVAGE Dose Levels: [redacted] mg/kg/day
97-1340[redacted]	CP-424,391-18 A SINGLE DOSE DERMAL TOXICITY STUDY IN RABBITS AND A SINGLE DOSE OCULAR IRRITATION STUDY IN RABBITS (Hazard Assessment Testing)
97-1340[redacted]	CP-424,391-18 SKIN SENSITIZATION TEST (GUINEA PIG MAXIMIZATION TEST)
RR-REG[redacted]	Nonclinical Safety Assessment of CP-424,391
	NON-CLINICAL TOXICOLOGY SUMMARY FOR CP-424,391
	NON-CLINICAL TOXICOLOGY SUMMARY FOR CP-424,391 (DRAFT)
	Table 10.1 Summary of Individual Non-Clinical Studies (1999) CP-424,391, IND-53,192 March 13, 1998 to March 12, 1999
	Table 10.1 Summary of Individual Non-Clinical Studies (2000) CP-424,391, IND-53,192 March 13, 1999 to March 12, 2000
	Table 10.1 Summary of Individual Non-Clinical Studies (2001) CP-424,391, IND-53,192 March 13, 2000 to March 12, 2001
	Table 10.1 Summary of Individual Non-Clinical Studies (2002) CP-424,391, IND-53,192 March 13, 2001 to March 12, 2002

臨床レポート

試験番号・ファイル名	試験タイトル・書類タイトル
A257[redacted]	Phase I, Investigator-Blind, Placebo-Controlled Study of the Clinical Pharmacology of CP-424,391 Following Single Oral Escalating Doses in Healthy, Young and Elderly Male Volunteers.
A257[redacted]	Phase I Double-Blind, Placebo Controlled Study of the Clinical Pharmacology of Multiple Doses of CP-424,391 in Healthy, Young and Elderly Male Subjects
A257[redacted]	Assay Validation and Performance of an HPLC/MS/MS Assay for Quantification of CP-424,391 and CP-420,866 in Human Plasma For [redacted] Clinical Study #257[redacted]
A257[redacted]	MINI-VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR THE DETERMINATION OF CP-424,391 IN PHOSPHATE BUFFERED SALINE (PBS) AND DETERMINATION OF PROTEIN BINDING FOR [redacted] STUDY 257[redacted]
A257[redacted]	Phase 1 Open, Pilot Study to Determine the Bioavailability of

	ZEALAND WHITE RABBITS ORAL GAVAGE Dose Levels: [redacted] mg/kg/day
97-1340[redacted]	CP-424,391-18 A SINGLE DOSE DERMAL TOXICITY STUDY IN RABBITS AND A SINGLE DOSE OCULAR IRRITATION STUDY IN RABBITS (Hazard Assessment Testing)
97-1340[redacted]	CP-424,391-18 SKIN SENSITIZATION TEST (GUINEA PIG MAXIMIZATION TEST)
RR-REG[redacted]	Nonclinical Safety Assessment of CP-424,391
	NON-CLINICAL TOXICOLOGY SUMMARY FOR CP-424,391
	NON-CLINICAL TOXICOLOGY SUMMARY FOR CP-424,391 (DRAFT)
	Table 10.1 Summary of Individual Non-Clinical Studies (1999) CP-424,391, IND-53,192 March 13, 1998 to March 12, 1999
	Table 10.1 Summary of Individual Non-Clinical Studies (2000) CP-424,391, IND-53,192 March 13, 1999 to March 12, 2000
	Table 10.1 Summary of Individual Non-Clinical Studies (2001) CP-424,391, IND-53,192 March 13, 2000 to March 12, 2001
	Table 10.1 Summary of Individual Non-Clinical Studies (2002) CP-424,391, IND-53,192 March 13, 2001 to March 12, 2002

Reports for clinical study

Study No. file name	Study title / Document title
A257[redacted]	Phase I, Investigator-Blind, Placebo-Controlled Study of the Clinical Pharmacology of CP-424,391 Following Single Oral Escalating Doses in Healthy, Young and Elderly Male Volunteers.
A257[redacted]	Phase I Double-Blind, Placebo Controlled Study of the Clinical Pharmacology of Multiple Doses of CP-424,391 in Healthy, Young and Elderly Male Subjects
A257[redacted]	Assay Validation and Performance of an HPLC/MS/MS Assay for Quantification of CP-424,391 and CP-420,866 in Human Plasma For [redacted] Clinical Study #257[redacted]
A257[redacted]	MINI-VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR THE DETERMINATION OF CP-424,391 IN PHOSPHATE BUFFERED SALINE (PBS) AND DETERMINATION OF PROTEIN BINDING FOR [redacted] STUDY 257[redacted]
A257[redacted]	Phase 1 Open, Pilot Study to Determine the Bioavailability of

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	CP-424,391 Administered intothe Stomach and Ascending Colon of Healthy, Young Male Volunteers.
A257[redacted]	Phase I Open Study to Compare the Bioavailability of Two Formulations of CP-424,391 After Single Dose Administration to Healthy, Young, Male Subjects
A257[redacted]	No title
A257[redacted]	Phase 1 Double-Blind, Placebo-Controlled, Multiple Dose Evaluation of CP-424,391 for Its Safety, Toleration and Efficacy in Calorically Restricted, Obese Men and Women.
A257[redacted]	Phase 1 Observer-Blind Study to Evaluate the Effect of CP-424,391 on Autonomic Reflexes after Single Dose Administration to Healthy, Young, Male Subjects.
A257[redacted]	Assay Verification Document[redacted] Study 257[redacted] Determination of CP-424,391 in Human Plasma
A257[redacted]	Phase I, Randomized, Double-Blind, Placebo-Controlled Study of the Clinical Pharmacology of CP-424,391 When Administered as Single Escalating Doses in Controlled Release Tablets to Healthy, Elderly Male Subjects.
A257[redacted]	Phase I, Randomized, Parallel Group Study of the Clinical Pharmacology of CP-424,391 When Administered Daily as Controlled Release Tablets to Healthy, Elderly Male Subjects.
A257[redacted]	Assay Verification Document[redacted] Study 257[redacted] Determination of CP-424,391 in Human Plasma
A257[redacted]	VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR THE DETERMINATION OF CP-424,391 AND CP-420,866 IN HUMAN PLASMA (HEPARIN)
A257[redacted]	Phase I, Open Study to Compare the Bioavailability of Two Controlled Release Tablet Formulations of CP-424,391 in Young, Healthy, Male and Female Subjects
A257[redacted]	Phase I, Open Study to Assess the Dose Proportionality of CP-424,391 When Administered as Two Controlled Release Tablet Formulations to Young, Healthy, Male and Female Subjects
A257[redacted]	AN OPEN STUDY TO EXAMINE THE METABOLISM AND EXCRETION OF [14C]CP-424,391 IN HEALTHY MALE

	CP-424,391 Administered intothe Stomach and Ascending Colon of Healthy, Young Male Volunteers.
A257[redacted]	Phase I Open Study to Compare the Bioavailability of Two Formulations of CP-424,391 After Single Dose Administration to Healthy, Young, Male Subjects
A257[redacted]	No title
A257[redacted]	Phase 1 Double-Blind, Placebo-Controlled, Mulliple Dose Evaluation of CP-424,391 for Its Safety, Toleration and Efficacy in Calorically Restricted, Obese Men and Women.
A257[redacted]	Phase 1 Observer-Blind Study to Evaluate the Effect of CP-424,391 on Autonomic Reflexes after Single Dose Administration to Healthy, Young, Male Subjects.
A257[redacted]	Assay Verification Document[redacted] Study 257[redacted] Determination of CP-424,391 in Human Plasma
A257[redacted]	Phase I, Randomized, Double-Blind, Placebo-Controlled Study of the Clinical Pharmacology of CP-424,391 When Administered as Single Escalating Doses in Controlled Release Tablets to Healthy, Elderly Male Subjects.
A257[redacted]	Phase I, Randomized, Parallel Group Study of the Clinical Pharmacology of CP-424,391 When Administered Daily as Controlled Release Tablets to Healthy, Elderly Male Subjects.
A257[redacted]	Assay Verification Document[redacted] Study 257[redacted] Determination of CP-424,391 in Human Plasma
A257[redacted]	VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR THE DETERMINATION OF CP-424,391 AND CP-420,866 IN HUMAN PLASMA (HEPARIN)
A257[redacted]	Phase I, Open Study to Compare the Bioavailability of Two Controlled Release Tablet Formulations of CP-424,391 in Young, Healthy, Male and Female Subjects
A257[redacted]	Phase I, Open Study to Assess the Dose Proportionality of CP-424,391 When Administered as Two Controlled Release Tablet Formulations to Young, Healthy, Male and Female Subjects
A257[redacted]	AN OPEN STUDY TO EXAMINE THE METABOLISM AND EXCRETION OF [14C]CP-424,391 IN HEALTHY MALE

	VOLUNTEERS.
A257[redacted]	Phase I, Non-Randomized, Open Study of the Effects of Multiple Doses of Ketoconazole on the Steady-State Pharmacokinetics of CP-424,391 in Healthy Male Subjects
A257[redacted] (Cancelled)	A RANDOMIZED, SPONSOR-OPEN, INVESTIGATOR AND SUBJECT BLINDED, TWO-PERIOD CROSSOVER PILOT STUDY OF MULTIPLE DOSES OF CAPROMORELIN (CP-424,391) IN MILD TO MODERATE ALZHEIMER'S DISEASE PATIENTS
A257[redacted] (Cancelled)	A RANDOMIZED, OPEN LABEL, MULTIPLE DOSE, TWO PERIOD CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS OF A CAPROMORELIN CONTROLLED RELEASE FORMULATION IN HEALTHY MALE VOLUNTEERS
A900[redacted]	A Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Single Doses of Capromorelin (CP-424,391) and Ghrelin on Esophageal Reflux Parameters, as Measured by Multi-Channel Intraluminal Impedance (MII) in Healthy Volunteers.
A257[redacted]	Phase II Double-Blind, Placebo-Controlled [redacted] Week Multiple Dose Evaluation of CP-424,391 for Its Safety, Toleration and Efficacy for Increasing IGF-1 in Older Normal Men and Women
A257[redacted]	Assay Verification Document[redacted] STUDY 257[redacted] DETERMINATION OF CP-424,391 IN HUMAN PLASMA
A257[redacted]	VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR THE DETERMINATION OF CP-424,391 AND CP-420,866 IN HUMAN PLASMA (HEPARIN)
A257[redacted]	A Randomized, Double Blind, Placebo Controlled, Five Parallel Group Study of the Effect of CP-424,391 on Physical Performance and Body Composition in Older Subjects.
A257[redacted]	PHASE II DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL, MULTIPLE DOSE EVALUATION OF CP-424,391 FOR ITS SAFETY, TOLERATION AND EFFICACY IN MEN AND WOMEN WITH MILD-TO-MODERATE HEART FAILURE.
A257[redacted]	Assay Verification Document[redacted] Study 257[redacted] Determination of CP-424,391 and CP-420,866 in Human Plasma
A257[redacted]	VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR

	VOLUNTEERS.
A257[redacted]	Phase I, Non-Randomized, Open Study of the Effects of Multiple Doses of Ketoconazole on the Steady-State Pharmacokinetics of CP-424,391 in Healthy Male Subjects
A257[redacted] (Cancelled)	A RANDOMIZED, SPONSOR-OPEN, INVESTIGATOR AND SUBJECT BLINDED, TWO-PERIOD CROSSOVER PILOT STUDY OF MULTIPLE DOSES OF CAPROMORELIN (CP-424,391) IN MILD TO MODERATE ALZHEIMER'S DISEASE PATIENTS
A257[redacted] (Cancelled)	A RANDOMIZED, OPEN LABEL, MULTIPLE DOSE, TWO PERIOD CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS OF A CAPROMORELIN CONTROLLED RELEASE FORMULATION IN HEALTHY MALE VOLUNTEERS
A900[redacted]	A Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Single Doses of Capromorelin (CP-424,391) and Ghrelin on Esophageal Reflux Parameters, as Measured by Multi-Channel Intraluminal Impedance (MII) in Healthy Volunteers.
A257[redacted]	Phase II Double-Blind, Placebo-Controlled, [redacted] Week Multiple Dose Evaluation of CP-424,391 for Its Safety, Toleration and Efficacy for Increasing IGF-1 in Older Normal Men and Women
A257[redacted]	Assay Verification Document[redacted] STUDY 257[redacted] DETERMINATION OF CP-424,391 IN HUMAN PLASMA
A257[redacted]	VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR THE DETERMINATION OF CP-424,391 AND CP-420,866 IN HUMAN PLASMA (HEPARIN)
A257[redacted]	A Randomized, Double Blind, Placebo Controlled, Five Parallel Group Study of the Effect of CP-424,391 on Physical Performance and Body Composition in Older Subjects.
A257[redacted]	PHASE II DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL, MULTIPLE DOSE EVALUATION OF CP-424,391 FOR ITS SAFETY, TOLERATION AND EFFICACY IN MEN AND WOMEN WITH MILD-TO-MODERATE HEART FAILURE.
A257[redacted]	Assay Verification Document[redacted] Study 257[redacted] Determination of CP-424,391 and CP-420,866 in Human Plasma
A257[redacted]	VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC MASS SPECTROMETRIC METHOD FOR

	THE DETERMINATION OF CP-424,391 AND CP-420,866 IN HUMAN PLASMA (HEPARIN)
A257[redacted]	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, 3 Parallel Group, Multicenter, [redacted] Week Study to Assess the Efficacy and Safety of CP-424,391 in Fibromyalgia Patients

CMC レポート

カテゴリー	ファイル数
Active Pharmaceutical Ingredient (API)	[redacted]
API Analytical	[redacted]
Drug Product	[redacted]
Drug Product Analytical	[redacted]
Regulatory CMC	[redacted]
Supply Chain	[redacted]
Placebo	[redacted]
Others	[redacted]

規制書類

IND	ファイル数
IND [redacted]	[redacted]
IND [redacted]	[redacted]
IND [redacted]	[redacted]
IND [redacted]	[redacted]

	THE DETERMINATION OF CP-424,391 AND CP-420,866 IN HUMAN PLASMA (HEPARIN)
A257[redacted]	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, 3 Parallel Group, Multicenter, [redacted] Week Study to Assess the Efficacy and Safety of CP-424,391 in Fibromyalgia Patients

CMC Reports

Category	Number of files
Active Pharmaceutical Ingredient (API)	[redacted]
API Analytical	[redacted]
Drug Product	[redacted]
Drug Product Analytical	[redacted]
Regulatory CMC	[redacted]
Supply Chain	[redacted]
Placebo	[redacted]
Others	[redacted]

Regulatory documents

IND	Number of files
IND [redacted]	[redacted]
IND [redacted]	[redacted]
IND [redacted]	[redacted]
IND [redacted]	[redacted]

資料2 サインオフシート

Check List and Sign-off for Asset Transfer from Pfizer to RaQualia

Program; Ghrelin agonist (Capromorelin)
Category; Clinical Program
Person in charge (Pfizer); [redacted], Development Team Leader
Person in charge (RaQualia); [redacted], Project Leader

1. List of Data to be transferred from Pfizer to RaQualia

Item #	Description	Check-in by receiver (date)	Check-in by receiver (signature)
RG-1	Investigational New Drug Application (IND) documents include Japan	Dec.9.2009	[redacted]
RG-2	New Drug Application (NDA) dossiers	NA	NA
RG-3	A complete set of letters and correspondences with regulatory agencies	Dec.9.2009	[redacted]
RG-4	Latest product labeling in US and EU countries	NA	NA
PS-1	Research reports and information for chemistry and pharmaceutics development for drug substances	Dec.9.2009	[redacted]
PS-2	Research reports and information for pharmaceutics development for drug products	Dec.9.2009	[redacted]
PS-3	Analytical reports and information including analytical method for drug substances and drug products	Dec.9.2009	[redacted]
PS-4	Reports and information regarding impurities.	Dec.9.2009	[redacted]
PS-5	A list of all third parties who supply GMP bulk, investigational products or finished product.	Dec.9.2009	[redacted]
PS-6	Reports associated with Quality Assurance for GMP compliance	Dec.9.2009	[redacted]
CMC-1	Cost of API bulk and final products	NA	NA
PD-1	Non-Clinical Pharmacology study protocols and reports	Dec.9.2009	[redacted]

資料2 サインオフシート

Check List and Sign-off for Asset Transfer from Pfizer to RaQualia

Program; Ghrelin agonist (Capromorelin)
Category; Clinical Program
Person in charge (Pfizer); [redacted], Development Team Leader
Person in charge (RaQualia); [redacted], Project Leader

1. List of Data to be transferred from Pfizer to RaQualia

Item #	Description	Check-in by receiver (date)	Check-in by receiver (signature)
RG-1	Investigational New Drug Application (IND) documents include Japan	Dec.9.2009	[redacted]
RG-2	New Drug Application (NDA) dossiers	NA	NA
RG-3	A complete set of letters and correspondences with regulatory agencies	Dec.9.2009	[redacted]
RG-4	Latest product labeling in US and EU countries	NA	NA
PS-1	Research reports and information for chemistry and pharmaceutics development for drug substances	Dec.9.2009	[redacted]
PS-2	Research reports and information for pharmaceutics development for drug products	Dec.9.2009	[redacted]
PS-3	Analytical reports and information including analytical method for drug substances and drug products	Dec.9.2009	[redacted]
PS-4	Reports and information regarding impurities.	Dec.9.2009	[redacted]
PS-5	A list of all third parties who supply GMP bulk, investigational products or finished product.	Dec.9.2009	[redacted]
PS-6	Reports associated with Quality Assurance for GMP compliance	Dec.9.2009	[redacted]
CMC-1	Cost of API bulk and final products	NA	NA
PD-1	Non-Clinical Pharmacology study protocols and reports	Dec.9.2009	[redacted]

PD-2	Non-Clinical Safety Pharmacology study protocols and reports	Dec.9.2009	
PK-1	Non-Clinical Pharmacokinetics protocols and reports (including radio-labeled studies)	Dec.9.2009	
PK-2	Reports on prediction of clinically efficacious concentrations, or pharmacokinetics, in humans	Dec.9.2009	
TX-1	Toxicology protocols and reports	Dec.9.2009	
CL-1	Clinical study protocols and reports (Phase I - II)	Dec.9.2009	
CL-2	Study protocol and reports for Clinical Studies in US/EU for approved indications and formulations	NA	NA
CL-3	Study protocol and reports for all Post-marketing studies by requested by the regulatory authority for approved indications and formulations	NA	NA
CL-4	Study protocols and reports for post-marketing studies for approved indications and formulations	NA	NA
CL-5	Study protocol and reports for clinical studies in US/EU for additional indications and formulations	NA	NA
CL-6	All Clinical Study Protocols and Reports conducted in Japan	NA	NA
MK-1	Latest five years sales record in US and EU	NA	NA
MK-2	Product promotion material	NA	NA

Note: This is a list of the information need to be stored in RaQualia data room for due diligence for out licensing. RaQualia will need to access additional information in future (e.g., raw data) during development and regulatory review process.

RG, regulatory; PS, pharmaceutical sciences; PD, pharmaco-dynamics; PK, pharmacokinetics and drug metabolism; TX, toxicology; CL, clinical; MK, Marketing; CMC, Chemistry Manufacture and Control

PD-2	Non-Clinical Safety Pharmacology study protocols and reports	Dec.9.2009	
PK-1	Non-Clinical Pharmacokinetics protocols and reports (including radio-labeled studies)	Dec.9.2009	
PK-2	Reports on prediction of clinically efficacious concentrations, or pharmacokinetics, in humans	Dec.9.2009	
TX-1	Toxicology protocols and reports	Dec.9.2009	
CL-1	Clinical study protocols and reports (Phase I - II)	Dec.9.2009	
CL-2	Study protocol and reports for Clinical Studies in US/EU for approved indications and formulations	NA	NA
CL-3	Study protocol and reports for all Post-marketing studies by requested by the regulatory authority for approved indications and formulations	NA	NA
CL-4	Study protocols and reports for post-marketing studies for approved indications and formulations	NA	NA
CL-5	Study protocol and reports for clinical studies in US/EU for additional indications and formulations	NA	NA
CL-6	All Clinical Study Protocols and Reports conducted in Japan	NA	NA
MK-1	Latest five years sales record in US and EU	NA	NA
MK-2	Product promotion material	NA	NA

Note: This is a list of the information need to be stored in RaQualia data room for due diligence for out licensing. RaQualia will need to access additional information in future (e.g., raw data) during development and regulatory review process.

RG, regulatory; PS, pharmaceutical sciences; PD, pharmaco-dynamics; PK, pharmacokinetics and drug metabolism; TX, toxicology; CL, clinical; MK, Marketing; CMC, Chemistry Manufacture and Control

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資料3 マテリアルリスト

Category	Compound ID	[redacted] Lot ID/Vendor Lot	Quantity	[redacted] Storage Location	Retest Date
API	CP-424391-18	E010003309 (AA0000266)	[redacted]kg	[redacted]	21-Dec-06
	CP-424391-18	E010003570 (AA0000266)	[redacted]kg	[redacted]	30-Jun-2007
CP-424,391-18[redacted]	D0401328	07-054047/CA-0760307	[redacted] tablets	[redacted] (US)	30-Apr-2009
CP-424,391-18[redacted]	D0401328	07-054047/CA-0760307	[redacted] tablets	[redacted]	30-Apr-2009
CP-424,391-18[redacted]	D0602987	07-055327/ CA-0850307	[redacted] tablets	[redacted]	Booked in 30-May-2007
CP-424,391-18[redacted]	D0703350	07-056669 / FP-07-031	[redacted] tablets	[redacted] (US)	30-Apr-2009
CP-424,391-18[redacted]	D0703350	07-056669 / FP-07-031	[redacted] tablets	[redacted]	30-Apr-2009
CP-424,391-18[redacted]	D0703350	07-056669 / FP-07-031	[redacted] tablets	[redacted]	30-Apr-2009
Placebo for CP-424,391-18[redacted]	D0703429	07-056671 / FP-07-030	[redacted] tablets	[redacted] (US)	30-Apr-2012
Placebo for CP-424,391-18[redacted]	D0703429	07-056671 / FP-07-030	[redacted] tablets	[redacted]	30-Apr-2012
Capromorel Tartrate[redacted]	G01191AB	03-001740 / ED-G-056-200	[redacted] tablets	[redacted] (US)	Booked in May-2003
Capromorel Tartrate[redacted]	G01191AB	03-001741 / ED-G-369-X00	[redacted] tablets	[redacted] (US)	Booked in May-2003
Capromorel Tartrate[redacted]	G01191AB	03-002749 / ED-G-369-X00	[redacted] tablets	[redacted] (US)	30-Apr-2004
CP-424,391-18[redacted]	G01192AA	03-001183 / ED-G-057-200	[redacted] tablets	[redacted]	Booked in Apr-03

資料3 Material List

Category	Compound ID	[redacted] Lot ID/Vendor Lot	Quantity	[redacted] Storage Location	Retest Date
API	CP-424391-18	E010003309 (AA0000266)	[redacted]kg	[redacted]	21-Dec-06
	CP-424391-18	E010003570 (AA0000266)	[redacted]kg	[redacted]	30-Jun-2007
CP-424,391-18[redacted]	D0401328	07-054047/CA-0760307	[redacted] tablets	[redacted] (US)	30-Apr-2009
CP-424,391-18[redacted]	D0401328	07-054047/CA-0760307	[redacted] tablets	[redacted]	30-Apr-2009
CP-424,391-18[redacted]	D0602987	07-055327/ CA-0850307	[redacted] tablets	[redacted]	Booked in 30-May-2007
CP-424,391-18[redacted]	D0703350	07-056669 / FP-07-031	[redacted] tablets	[redacted] (US)	30-Apr-2009
CP-424,391-18[redacted]	D0703350	07-056669 / FP-07-031	[redacted] tablets	[redacted]	30-Apr-2009
CP-424,391-18[redacted]	D0703350	07-056669 / FP-07-031	[redacted] tablets	[redacted]	30-Apr-2009
Placebo for CP-424,391-18[redacted]	D0703429	07-056671 / FP-07-030	[redacted] tablets	[redacted] (US)	30-Apr-2012
Placebo for CP-424,391-18[redacted]	D0703429	07-056671 / FP-07-030	[redacted] tablets	[redacted]	30-Apr-2012
Capromorel Tartrate[redacted]	G01191AB	03-001740 / ED-G-056-200	[redacted] tablets	[redacted] (US)	Booked in May-2003
Capromorel Tartrate[redacted]	G01191AB	03-001741 / ED-G-369-X00	[redacted] tablets	[redacted] (US)	Booked in May-2003
Capromorel Tartrate[redacted]	G01191AB	03-002749 / ED-G-369-X00	[redacted] tablets	[redacted] (US)	30-Apr-2004
CP-424,391-18[redacted]	G01192AA	03-001183 / ED-G-057-200	[redacted] tablets	[redacted]	Booked in Apr-03

				(US)	
CP-424,391-18 [redacted]	G01192AA	03-001192 / ED-G-370-X00	[redacted] tablets	[redacted] (US)	Booked in Apr-03
CP-424,391-18 [redacted]	G01192AA	03-001196 / ED-G-221-599	[redacted] tablets	[redacted] (US)	Booked in Apr-03
CP-424,391-18 [redacted]	G01192AA	03-002747 / ED-G-370-X00	[redacted] tablets	[redacted] (US)	30-Apr-2004
Placebo for Capromorel [redacted]	G01193AB	03-001194 / ED-G-365-X00	[redacted] tablets	[redacted] (US)	30-Noc-2005
Placebo for Capromorel [redacted]	G01193AB	03-002745 / ED-G-365-X00	[redacted] tablets	[redacted] (US)	1-Nov-2005
Placebo for CP-424,391-18 [redacted]	G01194AA	03-001172 / ED-G-366-X00	[redacted] tablets	[redacted] (US)	30-Nov-2005
Placebo for CP-424,391-18 [redacted]	G01194AA	03-002748 / ED-G-366-X00	[redacted] tablets	[redacted] (US)	1-Nov2005
Placebo for Capromorel [redacted]	G01438AA	03-001099 / ED-G-063-298	[redacted] tablets	[redacted] (US)	31-Dec-2003
Placebo for CP-424,391-18 [redacted]	G01626AA	03-001222 / ED-G-353-998	[redacted] tablets	[redacted] (US)	31-Oct-2003

				(US)	
CP-424,391-18 [redacted]	G01192AA	03-001192 / ED-G-370-X00	[redacted] tablets	[redacted] (US)	Booked in Apr-03
CP-424,391-18 [redacted]	G01192AA	03-001196 / ED-G-221-599	[redacted] tablets	[redacted] (US)	Booked in Apr-03
CP-424,391-18 [redacted]	G01192AA	03-002747 / ED-G-370-X00	[redacted] tablets	[redacted] (US)	30-Apr-2004
Placebo for Capromorel [redacted]	G01193AB	03-001194 / ED-G-365-X00	[redacted] tablets	[redacted] (US)	30-Noc-2005
Placebo for Capromorel [redacted]	G01193AB	03-002745 / ED-G-365-X00	[redacted] tablets	[redacted] (US)	1-Nov-2005
Placebo for CP-424,391-18 [redacted]	G01194AA	03-001172 / ED-G-366-X00	[redacted] tablets	[redacted] (US)	30-Nov-2005
Placebo for CP-424,391-18 [redacted]	G01194AA	03-002748 / ED-G-366-X00	[redacted] tablets	[redacted] (US)	1-Nov2005
Placebo for Capromorel [redacted]	G01438AA	03-001099 / ED-G-063-298	[redacted] tablets	[redacted] (US)	31-Dec-2003
Placebo for CP-424,391-18 [redacted]	G01626AA	03-001222 / ED-G-353-998	[redacted] tablets	[redacted] (US)	31-Oct-2003

資料4　特許リスト

RQ ID [redacted] ID)	Filing Date	Countries	Comments
P0005A (PC9918A)	[redacted]	Granted [redacted] US [redacted]	[redacted] patent
P0005B (PC9291A)	Dec 4, 1996	Granted [redacted] US [redacted]	Compound patent
P0005C (PC10464A)	Feb 25, 2000	Granted [redacted] US [redacted]	Synthetic process patent
P0005D (PC10845A)	[redacted]	Granted [redacted] US [redacted]	[redacted] patent

[redacted]

資料4　IP List

RQ ID [redacted] ID)	Filing Date	Countries	Comments
P0005A (PC9918A)	[redacted]	Granted [redacted] US [redacted]	[redacted] patent
P0005B (PC9291A)	Dec 4, 1996	Granted [redacted] US [redacted]	Compound patent
P0005C (PC10464A)	Feb 25, 2000	Granted [redacted] US [redacted]	Synthetic process patent
P0005D (PC10845A)	[redacted]	Granted [redacted] US [redacted]	[redacted] patent

[redacted]

EXHIBIT 42

RaQualia

Sign-off for Asset Transfer from Pfizer to RaQualia

We confirm that Pfizer has completed delivery of the key information (see attached check lists) and materials for "Ghrelin agonist" as described in Exhibit 2.5 (2-1) Trigger Events of RaQualia Pharma Inc. Share Subscription Agreement.

Atsushi Nagahisa, Ph.D.
President & CEO

12/15/2009
Date

Shinichi Koizumi, Ph.D.
Senior Vice President, Research & CSO

12/15/2009
Date

Tomoko Nii, Ph.D.
Senior Vice President, Development

12/15/2009
Date

EXHIBIT 43

[redacted]

差出人: [redacted] <[redacted]@gmail.com>
送信日時: 2010年5月24日月曜日 8:34
宛先: [redacted]
件名: Re: RaQualia Animal Health Opportunity

What is your starting point on what makes sense? It would be a deal even though it is animal health. Markets are about 10 percent the size of pharma but risk to market is lower. It may also help with the ipo.

Best, dr

Sent from my iPhone

On May 23, 2010, at 10:58 AM, "[redacted]" <[redacted]@raqualia.com> wrote:

[redacted]

Attached is a high-level summary of the programs. Both RQ-5 (Capromorelin) and [redacted] ([redacted] are ready for pivotal studies, and substantially de-risked with 1-year and 9-months GLP tox in dogs with NOAELs defined.

Let us know what you can do with the financial figures. If they are in the range that will make sense for both of us, then we should pursue. If not, at least we tried.

regards,

[redacted]

From: [redacted]@gmail.com [mailto:[redacted]@gmail.com]
Sent: Sunday, May 23, 2010 6:38 PM
To: [redacted]
Subject: Re: RaQualia Animal Health Opportunity

Thanks [redacted]

EXHIBIT 44

MINUTES OF THE MEETING OF THE BOARD OF DIRECTORS OF ARATANA THERAPEUTICS, INC.

February 24, 2011

A meeting of the Board of Directors (the ***"Board"***) of **ARATANA THERAPEUTICS, INC.**, a Delaware corporation (the ***"Company"***), was held on Thursday, February 24, 2011, at 1:30 p.m. Central Time, at 1901 Olathe Boulevard, Kansas City, Kansas 66103. Notice of the meeting was duly given or waived in accordance with the Company's bylaws.

CLINICAL UPDATE

Dr. Rhodes led a discussion regarding the Company's development program for AT-001, focusing particularly on the clinical progress to date. In addition, Dr. Rhodes discussed a proposed development program for AT-002, indicating that while management intends to present more detailed recommendations with respect to AT-002 in the future, the current focus remains on AT-001. Questions were asked and full discussion ensued.

ADJOURNMENT

There being no further business to come before the Board, upon motion duly made and seconded, the meeting was adjourned.

Respectfully submitted,

By: _____
Steven St. Peter
Secretary