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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| 18/307,718 | 01/11/2024 06:20:34 PM Z ET | 50535-709.307 |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Alma Goldchain |
| PATENT CENTER # | 63923093 | AUTHORIZED BY | Christina Hoong |
| CUSTOMER # | 21971 | FILING DATE | 04/26/2023 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| DA / 232415 | E20241AI21545224 | Christina Hoong |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1814 | STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER | 170.00 | 1 | 170.00 |
| | | | TOTAL AMOUNT: | $170.00 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **01/11/2024 06:09:38 PM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Alma Goldchain |
| PATENT CENTER # | 63926045 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Christina Hoong |

## Documents

**TOTAL DOCUMENTS: 3**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| 50535-709-307_Response_NFOA_Track One_asfiled.pdf | | 9 | - | 155 KB |
| 50535-709-307_Response_NFOA_Track One_asfiled-A....pdf | (1-1) | 1 | Amendment/Request for Reconsideration-After Non-Final Rejection | 96 KB |
| 50535-709-307_Response_NFOA_Track One_asfiled-CLM.pdf | (2-5) | 4 | Claims | 124 KB |
| 50535-709-307_Response_NFOA_Track One_asfiled-REM.pdf | (6-9) | 4 | Applicant Arguments/Remarks Made in an Amendment | 102 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| 50535-709-307_Response_NFOA_Track One_asfiled.pdf | 9577B586BD6FB55E8E9904965AFFD8065059709509BC3EBB768F63B62137273EF393B54A4C7DC79F48BBD198A4056D952D7CB9D2644F0567A9A0ABF07183BE11 |
| 50535-709-307_Response_NFOA_Track One_asfiled-A….pdf | AE225236AF4A1B0977B2FBCCF473C3522B0852D831CE9D45FD6EB794AA70C22FAE52BD172B4AFA60FD0765A96903C99CFBD1F1D210B95635A6C1566692106120 |
| 50535-709-307_Response_NFOA_Track One_asfiled-CLM.pdf | C42B232ED284C6C0671B6C476FE2636D074BB0E6F9EF05C6E46B410113C37BB562B38FB99546E7BD3DF3A2CF879750450CDF11726AB3A0D6EDCF7462A684DEDA |
| 50535-709-307_Response_NFOA_Track One_asfiled-REM.pdf | 022BBD9453FA6C0F9555243C40788F76D52F91ED800DBEFD63BD26BFA935F7A3A44022087F61F8316051B902515F6A37BA77B905758F67323C6DC7A5FA58C071 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re the Application of: | Art Unit: 1612 |
| Inventors: Alexis HOWERTON *et al.* | Examiner: Celeste A. RONEY |
| Serial No.: 18/307,718 | Confirmation No.: 9067 |
| Filing Date: April 26, 2023 | Customer No.: 021971 |
| Title: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS | |

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**RESPONSE TO NON-FINAL OFFICE ACTION**

Dear Commissioner:

This paper responds to the Non-Final Office Action mailed October 12, 2023, setting an initial due date of January 12, 2024. Applicants have replied within the shortened statutory period for reply. Accordingly, this response is timely filed, and no fees are believed to be due. However, in the event Applicants are incorrect in their assumption, please charge any additional fees due to Deposit Account No. 23-2415, referencing Docket No. 50535-709.307.

**Amendments to the Claims** begin on page **2**.

**Remarks** begin on page **6**.

**The Conclusion** is on page **9**.

## REMARKS

### Status of the Claims

Claims 1-21 were pending. Claim 1 is amended. Claim 16 is canceled. New claim 22 is added. Upon entry of the proposed claims, claims 1-15 and 17-22 will be under examination. Support for the amendments to the claims is found in the original claims and throughout the specification, in at least Example 2 of the specification. No new matter is introduced by any amendment made herein.

### Examiner Interview Summary

Applicant thanks Examiner Roney for speaking with patent agent Christina Hoong and patent attorney Rona Lamiquiz on January 5, 2024, regarding potential amendments to claim 1 to proceed towards allowance. Claim 1 is amended as proposed during the Examiner interview, which the Examiner has indicated will likely result in an allowance pending further search. As discussed, the dosage provided in claim 1 has an unexpected benefit of being more stable for shelf storage, which Grigoriadis et al. (US 2017/0020877 A1), Speisser et al. (J Clin Endocrinol Metabol, 2010, 95(9), 4133-4160), and Trapp et al. (Curr Opin Endocrinol Diabetes Obes, 2011, June, 18(3), 166-170) do not teach, suggest, or render obvious such claim element.

### Claim Rejections – 35 U.S.C. § 103

The Office rejected claims 1, 10, and 12-21 under 35 U.S.C. § 103 as being allegedly unpatentable over Grigoriadis et al., in view of Speiser et al., and further in view of Trapp et al.

Without conceding to the basis of the rejection and solely to expedite prosecution, Applicant has amended claim 1 to recite: "wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day, and wherein the CRF1 receptor antagonist is stable for storage for a minimum of six months."

As discussed in the interview, Grigoriadis et al. does not teach that the CRF1 receptor antagonist is stable for storage for a minimum of six months at the dosages described. In Example 2 of the pending application, CRF1 receptor antagonists are tested under various stability conditions, and it was found that the dosages were stable for a minimum of 6 months and that no adverse trends were observed under long term and accelerated conditions. The results found that there was no new

related substances, that could result from degradation, were observed for the stability studies, indicate the dosages are useful for long-term storage.

Applicant submits that claim 1, as amended, is non-obvious over Grigoriadis et al., in view of Speiser et al., and further in view of Trapp et al. since these references, either lone or in combination, do not teach, suggest, or render obvious all the elements of the instantly amended claim 1. Accordingly, Applicant respectfully requests the withdrawal of the pending § 103 rejection as applied to claim 1.

Claims 10, 12-15, and 17-21 depend either directly or indirectly from claim 1 and recite additional elements. Applicant submits that Grigoriadis et al., in view of Speiser et al. and further in view of Trapp et al. do not teach, suggest, or render obvious all elements of claims 10, 12-15, and 17-21. Accordingly, Applicant respectfully requests the withdrawal of the pending § 103 rejection as applied to claims 10, 12-15, and 17-21.

The Office rejected claims 2-9 under 35 U.S.C. § 103 as being allegedly unpatentable over Grigoriadis et al., in view of Speiser et al., further in view of Trapp et al., and further in view of Nella et al. (J Clin Endocrinol Metab, December 2016, 101(12), 4690-4698).

Without conceding to the basis of the rejection and solely to expedite prosecution, Applicant has amended claim 1 as described above. Applicant submits that the cited references do not teach, suggest, or render obvious all the elements of claim 1 as instantly amended as described above. Nella et al. does not cure such deficiency.Since claims 2-9 depend from claim 1 and recite additional elements, they are also non-obvious over the cited references. Accordingly, Applicant respectfully requests the withdrawal of the pending § 103 rejection as applied to claims 2-9.

The Office rejected claim 11 under 35 U.S.C. § 103 as being allegedly unpatentable over Grigoriadis et al., in view of Speiser et al., further in view of Trapp et al., and further in view of Chen et al. (USPN 8,030,304 B2).

Without conceding to the basis of the rejection and solely to expedite prosecution, Applicant has amended claim 1 as described above. Applicant submits that the cited references do not teach, suggest, or render obvious all the elements of claim 1 as instantly amended. Chen et al. does not cure such deficiency. Since claim 11 depends from claim 1 and recite additional elements, they are also non-obvious over the cited references. Accordingly, Applicant respectfully requests the withdrawal of the pending § 103 rejection as applied to claim 11.

**Nonstatutory Double Patenting**

The Office provisionally rejected claims 1-21 on the ground of nonstatutory double patenting as allegedly unpatentable over claims 181-201 of copending U.S. App. No. 18/078,649 in view of Grigoriadis et al. and Trapp et al.

Without conceding to the basis of the rejection and solely to expedite prosecution, Applicant submits concurrently herewith a terminal disclaimer over the '649 application. Accordingly, Applicant respectfully requests the withdrawal of the nonstatutory double patenting rejection.

The Office rejected claims 1-21 on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-19 of U.S. Pat. No. 11,007,201 B2 in view of Grigoriadis et al. and Speiser et al.

Without conceding to the basis of the rejection and solely to expedite prosecution, Applicant submits concurrently herewith a terminal disclaimer over the '201 patent. Accordingly, Applicant respectfully requests the withdrawal of the nonstatutory double patenting rejection.

The Office rejected claims 1-21 on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-19 of U.S. Pat. No. 11,311,549 B2 in view of Grigoriadis et al. and Speiser et al.

Without conceding to the basis of the rejection and solely to expedite prosecution, Applicant submits concurrently herewith a terminal disclaimer over the '549 patent. Accordingly, Applicant respectfully requests the withdrawal of the nonstatutory double patenting rejection.

## CONCLUSION

Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned attorney. The Commissioner is hereby authorized to charge any fees that may be required or credit any overpayment to Deposit Account No. 23-2415, referencing Attorney Docket No. 50535-709.305.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: January 11, 2024

By: /Christina Hoong/
Christina Hoong
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Customer No. 021971

## AMENDMENTS TO THE CLAIMS

This listing of claims replaces all prior versions and listing of claims in the above-referenced patent application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed.

**Listing of the Claims**

1. (Currently Amended) A method for treating congenital adrenal hyperplasia (CAH) in a human, comprising:

administering to said human a therapeutically-effective amount of a $CRF_1$ receptor antagonist or a pharmaceutically acceptable salt thereof,

wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and

administering to said human a second dose of a glucocorticoid, wherein said second dose of a glucocorticoid is reduced compared to said first dose of a glucocorticoid,

wherein an androstenedione (A4) level in said subject is reduced from baseline, or

wherein an adrenocorticotropic hormone (ACTH) level in said subject is reduced from baseline, or

wherein a 17-hydroxyprogesterone (17-OHP) level in said subject is reduced from baseline,

wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day, and wherein said CRF1 receptor antagonist is stable for storage for a minimum of six months.

2. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 5% from baseline.

3. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 10% from baseline.

4. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP

level in said human is reduced by at least 15% from baseline.

5. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 20% from baseline.

6. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 25% from baseline.

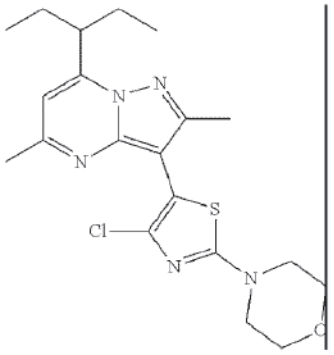
7. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 24 hours.

8. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 4 weeks.

9. (Original) The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 6 weeks.

10. (Original) The method of claim 1, wherein said administering of said first dose of said glucocorticoid is concurrently or sequentially within 2 hours of said administering of said therapeutically- effective amount of a **$CRF_1$** receptor antagonist or a pharmaceutically acceptable salt thereof.

11. (Original) The method of claim 1, wherein said **$CRF_1$** receptor antagonist or a pharmaceutically acceptable salt thereof is Compound 1:



or a pharmaceutically acceptable salt thereof.

12. (Original) The method of claim 1, wherein said glucocorticoid is selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

13. (Original) The method of claim 1, wherein said glucocorticoid is hydrocortisone.

14. (Original) The method of claim 1, wherein said first dose of said glucocorticoid comprises a supraphysiologic amount of said glucocorticoid.

15. (Original) The method of claim 1, wherein said second dose of said glucocorticoid comprises a physiologic amount of said glucocorticoid.

16. (Canceled)

17. (Original) The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is orally administered.

18. (Original) The method of claim 17, wherein said oral administration is once a day.

19. (Original) The method of claim 17, wherein said oral administration is twice a day.

20. (Original) The method of claim 1, wherein said first dose is a first daily dose and said second dose is a second daily dose.

21. (Original) The method of claim 1, wherein said second dose of said glucocorticoid is at least about 5%, at least about 10%, or at least about 20% lower than said first dose of said glucocorticoid.

22. (New) The method of claim 1, wherein said CRF1 receptor antagonist is stable between about 25 ºC and about 40 ºC.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>18/307,718 | Filing Date<br>04/26/2023 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☑ LARGE ☐ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $100 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $480 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 01/11/2024 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * 21 | Minus | ** 21 | = 0 | | x $100 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 1 | Minus | *** 3 | = 0 | | x $480 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | SLIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /DESHONNE T. MARTINO-RAY/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

21971 7590 01/11/2024
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| RONEY, CELESTE A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 01/11/2024 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

| *Applicant-Initiated Interview Summary* | Application No. 18/307,718 | Applicant(s) HOWERTON et al. | | |
|---|---|---|---|---|
| | Examiner CELESTE A RONEY | Art Unit 1612 | AIA (First Inventor to File) Status Yes | Page 1 of 1 |

| All Participants (applicant, applicants representative, PTO personnel) | Title | Type |
|---|---|---|
| CELESTE A RONEY | Primary Examiner | Video Conference |
| Christina Hoong | Attorney | |
| Rona Lamiquiz | Attorney of Record | |

**Date of Interview:** 05 January 2024

**Issues Discussed:**

**35 U.S.C. 103**

Applicant sought to clarify the invention from the closest prior art, Grigoriadis et al (of record). Applicant proposed claim amendments, and discussed unexpected results, to distinguish the instant claim 16 from the prior art. The Examiner advised the Applicant to provide evidence of a criticality of the claim 16 dose range, and to amend claim 1. The Examiner will search and consider all claim amendments, and evidence, upon receipt. Patentability was discussed, but not agreed upon, pending the Applicant's evidence and amendments.

| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | |
|---|---|

**Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04**
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

**Applicant recordation instructions:** The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

**Examiner recordation instructions:** Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-20050209250 | 09-22-2005 | ROMANO; Steve | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

| Complete if Known | |
|---|---|
| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | U.S. Patent No. 10,849,908 - Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review dated December 1, 2023. 57 pages. | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 4

| Complete if Known | |
|---|---|
| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Christina Hoong/ | Date (YYYY-MM-DD) | 2024-01-25 |
| Name/Print | Christina Hoong | Registration Number | 77,769 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis | Group Art Unit: | 1612 |
| Serial Number: | US18/307,718 | Examiner: | RONEY; Celeste A. |
| Filing or 371 (c) Date: | 2023-04-26 | **CONFIRMATION NO:** | **9067** |
| Title: | CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS | | |

**FILED ELECTRONICALLY ON: January 25, 2024**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $260.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $260.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.50535-709.307).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 25, 2024

By: /Christina Hoong/
Christina Hoong
Reg. No. 77,769

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **01/25/2024 11:18:03 AM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Caitlin Newland |
| PATENT CENTER # | 64081829 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Christina Hoong |

## Documents

**TOTAL DOCUMENTS: 3**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| IDS_50535-709_307_01-25-2024.pdf | | 8 | - | 222 KB |
| IDS_50535-709_307_01-25-2024-TRAN.LET.pdf | (1-4) | 4 | Transmittal Letter | 146 KB |
| IDS_50535-709_307_01-25-2024-IDS.pdf | (5-8) | 4 | Information Disclosure Statement (IDS) Form (SB08) | 159 KB |
| NPL_NEUROCRINE-v-SPRUCE-Decision-Granting-Institution-US10849908-2023-12-01.pdf | | 57 | Non Patent Literature | 877 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| IDS_50535-709_307_01-25-2024.pdf | 388F9BCFC570BCDABC8195BF398044D71C1155A3A091E2C49E2B9CE101D96BAE4DFF2DF367C352842513F13EACBD39DE57DAE9922D3E32E14378E4F911816D46 |
| IDS_50535-709_307_01-25-2024-TRAN.LET.pdf | 373A640A8166232752C118E24DAD6716BEFDBCA3B49DA6A95B48CAD465007D14DB24482016D58352D9824E25A83138ABBB88A63D7CEF9B721D1118DDC3F94912 |
| IDS_50535-709_307_01-25-2024-IDS.pdf | A04DAADC1D67378DF4939D1A132D57C546005851A9F0E10728749AD9DC101A0597030C6F5423549EC6A52717A6435F7EA4CC9FA84A7456D3EB6BBCF6AE4C4938 |
| NPL_NEUROCRINE-v-SPRUCE-Decision-Granting-Institution-US10849908-2023-12-01.pdf | FCCC6065C0425C3F0528F3495C3A3D94D5CE5F806E139089DD38BD546E2D59D7C6DF5F670BB020EA44B904C48D45D7F68775B834F00C7426F6764D73589010C4 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **01/25/2024 11:18:03 AM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Caitlin Newland |
| PATENT CENTER # | 64081829 | AUTHORIZED BY | Christina Hoong |
| CUSTOMER # | 21971 | FILING DATE | 04/26/2023 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| **DA / 232415** | **E20241OB19035332** | **Caitlin Newland** |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1806 | SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT | 260.00 | 1 | 260.00 |
| | | | **TOTAL AMOUNT:** | **$260.00** |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

# NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 02/14/2024

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| RONEY, CELESTE A | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 02/14/2024

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 05/14/2024 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.**

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 02/14/2024
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

| (Typed or printed name) |
|---|
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 05/14/2024 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| RONEY, CELESTE A | 1612 | 424-489000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____



PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

21971 7590 02/14/2024

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| RONEY, CELESTE A | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 02/14/2024

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

| Notice of Allowability | Application No. 18/307,718 | Applicant(s) HOWERTON et al. | |
|---|---|---|---|
| | Examiner CELESTE A RONEY | Art Unit 1612 | AIA (FITF) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to amended claims and remarks, each dated 01/11/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-15 and 17-22 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/6/26; 1/25/24.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | CELESTE A RONEY | 1612 |

| CPC | | | | | | |
|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Version** |
| A61K | / | 31 | / | 5377 | F | 2013-01-01 |
| A61P | / | 5 | / | 00 | I | 2018-01-01 |
| A61K | / | 9 | / | 14 | I | 2013-01-01 |
| A61K | / | 9 | / | 4825 | I | 2013-01-01 |
| A61K | / | 9 | / | 48 | I | 2013-01-01 |
| A61P | / | 5 | / | 24 | I | 2018-01-01 |
| A61K | / | 31 | / | 573 | I | 2013-01-01 |
| C07D | / | 487 | / | 04 | I | 2013-01-01 |
| A61P | / | 5 | / | 38 | I | 2018-01-01 |

| CPC Combination Sets | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Set** | **Ranking** | **Version** |
| A61K | / | 31 | / | 5377 | I | 1 | 1 | 2013-01-01 |
| A61K | / | 2300 | / | 00 | I | 1 | 2 | 2013-01-01 |
| A61K | / | 31 | / | 573 | I | 2 | 1 | 2013-01-01 |
| A61K | / | 2300 | / | 00 | I | 2 | 2 | 2013-01-01 |

| NONE | | **Total Claims Allowed:** | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | 07 February 2024 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | none |

U.S. Patent and Trademark Office — Part of Paper No.: 20240207

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | CELESTE A RONEY | 1612 |

| INTERNATIONAL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|
| **CLAIMED** | | | | | |
| A61K31/5377 | / | 31 | / | 5377 | |
| A61P5/00 | / | 5 | / | 00 | |
| C07D487/04 | / | 487 | / | 04 | |

| NON-CLAIMED | | | | |
|---|---|---|---|---|
| | / | | / | |

| US ORIGINAL CLASSIFICATION | |
|---|---|
| **CLASS** | **SUBCLASS** |
| | |

| CROSS REFERENCES(S) | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **SUBCLASS (ONE SUBCLASS PER BLOCK)** | | | | | |
| | | | | | | |

| NONE | | **Total Claims Allowed:** | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | 07 February 2024 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | none |

U.S. Patent and Trademark Office — Part of Paper No.: 20240207

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | CELESTE A RONEY | 1612 |

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

**CLAIMS**

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 10 | 10 | 19 | 20 | | | | | | | | | | |
| 2 | 2 | 11 | 11 | 20 | 21 | | | | | | | | | | |
| 3 | 3 | 12 | 12 | 21 | 22 | | | | | | | | | | |
| 4 | 4 | 13 | 13 | | | | | | | | | | | | |
| 5 | 5 | 14 | 14 | | | | | | | | | | | | |
| 6 | 6 | 15 | 15 | | | | | | | | | | | | |
| 7 | 7 | 16 | 17 | | | | | | | | | | | | |
| 8 | 8 | 17 | 18 | | | | | | | | | | | | |
| 9 | 9 | 18 | 19 | | | | | | | | | | | | |

| NONE | | **Total Claims Allowed:** | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | 07 February 2024 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | none |

U.S. Patent and Trademark Office Part of Paper No.: 20240207

## PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 638 | crf1 adj2 receptor adj2 antagonist | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/02/07 12:18 PM |
| L2 | 1 | crf1 adj2 receptor adj2 antagonist WITH (stab$5) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/02/07 12:19 PM |
| L3 | 350 | crf1 adj2 receptor adj2 antagonist AND (stab$5) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/02/07 12:19 PM |
| L4 | 3963 | corticotropin adj2 releasing adj2 factor adj2 antagonist AND | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, | OR | ON | ON | 2024/02/07 12:35 PM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | (stab$5) | CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L5 | 1291 | corticotropin adj2 releasing adj2 factor adj2 receptor adj2 antagonist AND (stab$5) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/02/07 12:35 PM |
| L6 | 64 | corticotropin adj2 releasing adj2 factor adj2 receptor adj2 antagonist AND (stab$5) AND congenital adj2 adrenal adj2 hyperplasia | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/02/07 12:36 PM |
| L7 | 64 | L6 AND ( (C07D487/04 OR C07D231/54 OR C07D233/20 OR C07D417/04 OR A61P5/38 OR A61P5/24 OR A61P5/00 OR A61P25/22 OR A61P15/08 OR A61P25/20 OR A61P25/24 OR A61P25/00 OR | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, | OR | ON | ON | 2024/02/07 03:33 PM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | A61P3/00 OR<br>A61P25/28 OR<br>A61P1/04 OR<br>A61P15/10 OR<br>A61P25/06 OR<br>A61P25/08 OR<br>A61P25/32 OR<br>A61P25/36 OR<br>A61P29/00 OR<br>A61P3/04 OR<br>A61P35/00 OR<br>A61P37/08 OR<br>A61P9/12 OR<br>A61P15/00 OR<br>A61P25/02 OR<br>A61P25/04 OR<br>A61P43/00 OR<br>A61P1/00 OR<br>A61P13/12 OR<br>A61P15/06 OR<br>A61P21/00 OR<br>A61P25/30 OR<br>A61K31/5377 OR<br>A61K9/14 OR<br>A61K9/4825 OR<br>A61K9/48 OR<br>A61K2300/00 OR<br>A61K31/573 OR<br>A61K9/2009 OR<br>A61K9/2027 OR<br>A61K9/2054 OR<br>A61K9/0053 OR<br>A61K9/1635 OR<br>A61K9/2077 OR<br>A61K9/2095 OR<br>A61K9/4816 OR<br>A61K31/536 OR<br>A61K31/4985 OR<br>A61K45/06 OR<br>A61K31/427 OR<br>A61K31/519 OR<br>A61K38/00 OR<br>A61K31/495 OR<br>A61K31/4166 OR<br>A61K31/53 OR<br>A61K9/20 OR<br>A61K9/2068).cpc.) | TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |

## PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | Examiner | Art Unit |
| | CELESTE A RONEY | 1612 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61K31/5377; A61P5/38; A61P5/00; A61P5/24; A61K9/14; A61K9/48; A61K9/4825; A61K31/573; C07D487/04 further limited by CAH and CRF1 receptor antagonist and glucocorticoid and baseline and reduced | 10/04/2023 | CR |
| A61K31/5377; A61P5/38; A61P5/00; A61P5/24; A61K9/14; A61K9/48; A61K9/4825; A61K31/573; C07D487/04 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| Search Notes | Date | Examiner |
| palm inventor search. google (patents and scholar) and PE2E searches further limited by CAH and CRF1 receptor antagonist and glucocorticoid and baseline and reduced | 10/04/2023 | CR |
| palm inventor search. google (patents and scholar) and PE2E searches further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |

| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | |
|---|---|

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | Examiner | Art Unit |
| | CELESTE A RONEY | 1612 |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| A61K31 | 5377 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61P5 | 38 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61P5 | 00 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61P5 | 24 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61K9 | 14 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61K9 | 48 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61K9 | 4825 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61K31 | 573 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| C07D487 | 04 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |

| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-20050209250 | 09-22-2005 | ROMANO; Steve | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 02/07/2024 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

| Complete if Known | |
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| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | U.S. Patent No. 10,849,908 - Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review dated December 1, 2023. 57 pages. | ☐ |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 02/07/2024 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Christina Hoong/ | Date (YYYY-MM-DD) | 2024-01-25 |
| Name/Print | Christina Hoong | Registration Number | 77,769 |

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/CELESTE A RONEY/ 02/07/2024

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

/CELESTE A RONEY/ 02/07/2024

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | 001 | WO-2005079868-A2 | 09-01-2005 | SB PHARMCO INC [US], et al. | | ☐ |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 02/07/2024 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Sheet 2 of 4

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| Application Number | US18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

## NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | ABCAM. CP 154526 hydrochloride, non-peptide CRF1 receptor antagonist ab141429. Product datasheet. Retrieved online on September 19, 2023 at: https://www.abcam.com/products/biochemicals/cp-154526-hydrochloride-non-peptide-crf1-receptor-antagonist-ab141429.html. 2 pages. | ☐ |
| | 002 | CHEN, C. Recent Advances in Small Molecule Antagonists of the Corticotropin-Releasing Factor Type-1 Receptor-Focus on Pharmacology and Pharmacokinetics. Current Medicinal Chemistry, 2006, 13, 1261-1282. | ☐ |
| | 003 | MILLION et al. A novel water-soluble selective CRF1 receptor antagonist, NBI 35965, blunts stress-induced visceral hyperalgesia and colonic motor function in rats. Brain Research, Vol. 985, Issue 1, 2003, pages 32-42. | ☐ |
| | 004 | MORABBI et al. Pexacerfont as a CRF1 antagonist for the treatment of withdrawal symptoms in men with heroin/methamphetamine dependence: a randomized, double-blind, placebo-controlled clinical trial. International Clinical Psychopharmacology 2017, Vol 00, No 00. 9 pages. | ☐ |
| | 005 | U.S. Serial No. 16/639,540 Office Action dated September 28, 2023. | ☐ |
| | 006 | U.S. Serial No. 18/078,649 Office Action dated September 8, 2023. | ☐ |
| | 007 | ZORRILLA et al. Progress in corticotropin-releasing factor-1 antagonist development. NIH Public Access - Author Manuscript provided (2011). 24 pages. Published in final edited form as: Drug Discov Today 2010; 15(9-10): 371-383. | ☐ |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 02/07/2024 |
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| Examiner Name | RONEY; Celeste A. |
| Attorney Docket Number | 50535-709.307 |

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Christina Hoong/ | Date (YYYY-MM-DD) | 2023-10-6 |
| Name/Print | Christina Hoong | Registration Number | 77,769 |

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/CELESTE A RONEY/ 02/07/2024

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

/CELESTE A RONEY/ 02/07/2024

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

# Web Search History

| date, time | web site | search string |
|---|---|---|
| 2/7/2024 12:13:26 PM | Google Scholar | (CRF1-receptor-antagonist)(storage-stable)(stability) |
| 2/7/2024 12:13:26 PM | Google Patents | Search Term 1<br>(CRF1-receptor-antagonist)(storage-stable)(stability) |

TO: patentdocket@wsgr.com
FROM: noreply@uspto.gov
CC: patentcenter_eofficeaction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - e-Postcard Notification for Customer Number 21971

Wed Feb 21 05:37:56 EST 2024

Dear Patent Center Customer:

Correspondence Address:

WILSON SONSINI GOODRICH &ROSATI
650 PAGE MILL ROAD
PALO ALTO,CALIFORNIA,94304-1050
UNITED STATES

An email notification regarding the correspondence was sent to the following email address(es) associated with customer number 21971:

patentdocket@wsgr.com

This is a courtesy reminder that new correspondence is available for the application. If you have not done so already, please review the correspondence listed below. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

| Application | Document | Mailroom Date | Attorney Docket No. |
|---|---|---|---|
| 18307718 | 1449 | 02/14/2024 | 50535-709.307 |
| 16902745 | A.NE.AFCP.D | 02/14/2024 | 53065-702.301 |
| 17111765 | NOA | 02/14/2024 | 62879-703.202 |
| 17111765 | 892 | 02/14/2024 | 62879-703.202 |
| 17939774 | CTNF | 02/14/2024 | 56396-718.301 |
| 17522284 | CTNF | 02/14/2024 | 63111-703.302 |
| 17522284 | 1449 | 02/14/2024 | 63111-703.302 |
| 18052880 | NOA | 02/14/2024 | 55495-808.302 |
| 18052880 | 892 | 02/14/2024 | 55495-808.302 |
| 16902745 | NOA | 02/14/2024 | 53065-702.301 |
| 16773625 | CTFR | 02/14/2024 | 50741-703.302 |
| 16773625 | 892 | 02/14/2024 | 50741-703.302 |
| 16773625 | 1449 | 02/14/2024 | 50741-703.302 |
| 16773625 | 1449 | 02/14/2024 | 50741-703.302 |
| 16773625 | 1449 | 02/14/2024 | 50741-703.302 |
| 17820811 | CTRS | 02/14/2024 | 53676-729.307 |
| 17820811 | 1449 | 02/14/2024 | 53676-729.307 |
| 17508128 | NOA | 02/14/2024 | 56884-729.302 |
| 18513066 | CTNF | 02/14/2024 | 54626-701.501 |
| 18513066 | 892 | 02/14/2024 | 54626-701.501 |
| 18513066 | 1449 | 02/14/2024 | 54626-701.501 |
| 18513066 | 1449 | 02/14/2024 | 54626-701.501 |
| 18123751 | EXIN | 02/14/2024 | 56075-703.301 |
| 18051125 | NOA | 02/14/2024 | 47134-737.401 |
| 18051125 | 1449 | 02/14/2024 | 47134-737.401 |
| 17232987 | CTFR | 02/14/2024 | 56884-772.201 |
| 17232987 | 892 | 02/14/2024 | 56884-772.201 |
| 18364775 | 892 | 02/14/2024 | 60964-702.301 |
| 18364775 | 1449 | 02/14/2024 | 60964-702.301 |
| 18052898 | NOA | 02/14/2024 | 45532-742.301 |
| 18052898 | 1449 | 02/14/2024 | 45532-742.301 |

| | | | |
|---|---|---|---|
| 18364775 | CTFR | 02/14/2024 | 60964-702.301 |
| 16605936 | CTNF | 02/14/2024 | 53676-715.831 |
| 17939774 | 1449 | 02/14/2024 | 56396-718.301 |
| 17522284 | 892 | 02/14/2024 | 63111-703.302 |
| 18307718 | NOA | 02/14/2024 | 50535-709.307 |
| 18307718 | 1449 | 02/14/2024 | 50535-709.307 |

To view your correspondence online, please sign in to Patent Center and then select Workbench/View correspondence. Or to update your email addresses, select Manage/Manage customer numbers.

If you have any questions, please contact the Patent Electronic Business Center (EBC) at ebc@uspto.gov or 866-217-9197 Monday – Friday, 6 a.m. to midnight ET.

Please do not reply to this email as it was sent from an unmonitored mailbox.

Sincerely,

The Patent Center Team

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| 18/307,718 | 05/10/2024 06:52:56 PM Z ET | 50535-709.307 |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | James Brady |
| PATENT CENTER # | 65480261 | AUTHORIZED BY | Christina Hoong |
| CUSTOMER # | 21971 | FILING DATE | 04/26/2023 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| DA / 232415 | E202450I53478075 | James Brady |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1501 | UTILITY ISSUE FEE | 1200.00 | 1 | 1200.00 |
| | | | TOTAL AMOUNT: | $1,200.00 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage

submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 02/14/2024
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

| | |
|---|---|
| James Brady | (Typed or printed name) |
| /James Brady/ | (Signature) |
| May 10, 2024 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 05/14/2024 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| RONEY, CELESTE A | 1612 | 424-489000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Wilson Sonsini Goodrich & Rosati
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Spruce Biosciences, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): South San Francisco, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Christina Hoong/ Date May 10, 2024

Typed or printed name Christina Hoong Registration No. 77,769



PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Alexandria, VA 22313 - 1450
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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **05/10/2024 06:52:56 PM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | James Brady |
| PATENT CENTER # | 65480261 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Christina Hoong |

## Documents

**TOTAL DOCUMENTS: 1**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| 50535-709-307-issue-fee-transmittal-05-10-2024.pdf | 1 | Issue Fee Payment (PTO-85B) | 133 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| 50535-709-307-issue-fee-transmittal-05-10-2024.pdf | EA86B6CB2BB0CAF02CB4B1F49555C53ABB5B6E05F629A5E518EF306393BDDD5549D5CFFDD8DF04BB601E8331CA5C816845084A98FFF75E79866AA22310D3CEB5 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized

by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 06/11/2024 | 12005065 | 50535-709.307 | 9067 |

21971 7590 05/22/2024

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Alexis HOWERTON, South San Francisco, CA;
Hal GERBER, South San Francisco, CA;
Michael HUANG, South San Francisco, CA;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Spruce Biosciences, Inc., South San Francisco, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **06/06/2024 04:32:24 PM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | 12005065 |
| CONFIRMATION # | 9067 | FILED BY | Kaia Parenti |
| PATENT CENTER # | 65861545 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | - |

## Documents

**TOTAL DOCUMENTS: 6**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| petition-request.pdf | 2 | ePetition Request Form | 31 KB |
| Spruce_50535-709_307_1st_QPIDS 4855-8409-5942 v.1.pdf | 2 | Quick Path Information Disclosure Statement | 174 KB |
| NPL_US18078649_OA_21MARCH2024.pdf | 10 | Non Patent Literature | 577 KB |
| NPL_US16639540_OA_28March2024-.pdf | 11 | Non Patent Literature | 652 KB |
| Spruce_50535-709_307_IDS_SB08_202406 | 2 | Information Disclosure Statement (IDS) Form (SB08) | 103 KB |

06_filing_with_QPIDS.pdf

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

| | | | |
|---|---|---|---|
| Spruce_50535-709_307_RCE_FilingWithQPIDS.pdf | 3 | Request for Continued Examination (RCE) | 50 KB |

Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| petition-request.pdf | 1A50F20A786D1CC4D6F85F9E881C8BC8BCC6AB2F69AF5EB68DA3CF3B533A3952AB7ED1DBF78FD6908047A1423006FFD69019F90E7703BCF99132983FCEF781B3 |
| Spruce_50535-709_307_1st_QPIDS 4855-8409-5942 v.1.pdf | AD9C8AC582FF4BF45546D9F87F9B218A1BD299C78D229E9ABC110ED5DAE86365916EF4A5EF591AFC1A5F80B864BF82ECFAADBF64060741BA9DA2CFF7FFB46855 |
| NPL_US18078649_OA_21MARCH2024.pdf | F8D7DF19E0ACF41F2A8CA8AF434D7D8C635DA3DDE1A3BC379C367469E51B5A9AF73E7A6EA4F442AD602D22D536A0556DFCC4C4F3EEB5EEC086DA089B2E6AE2C0 |
| NPL_US16639540_OA_28March2024-.pdf | 52C52486CEEF02F8267AF54925E34AE8657E46338A4CC8CC46AA65B7F306505675E804578997DE567DD7B4ABA09E35A29DAA36361D61105902CA67C07D2B4343 |
| Spruce_50535-709_307_IDS_SB08_20240606_filing_with_QPIDS.pdf | 19C8725C21709F4E1F9192096D311F6AEE3634B50B6C60FF748A1CAB3F86D0E729492E42B82CE5EF51B271928F198C99B46D84668272EC569A3C9D946B11D277 |
| Spruce_50535-709_307_RCE_FilingWithQPID | B23C1EF8064EB006D5904BD808297D9C9841BAB52E474FD952BB9266B61EF0A301ACE6B9CD545D453D67EACAE7CF4694A |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

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UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# GRANT LETTER

| APPLICATION # | DECISION DATE | DECISION ON PETITION # | ATTORNEY DOCKET NUMBER |
|---|---|---|---|
| 18/307,718 | 06/06/2024 | | 50535-709.307 |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

**In re Application of Alexis HOWERTON**

This is an electronic decision on the petition under , filed June 06, 2024 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED.**

**Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.**

The application is being referred to Technology Center AU for

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions

Doc Code: QPIDS.REQ
Document Description: Quick Path Information Disclosure Statement

PTO/SB/09 (09-18)

**CERTIFICATION AND REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM**

| Non-Provisional Application Number: 18/307,718 | Filing Date: 4/26/2023 |
|---|---|
| First Named Inventor: Alexis HOWERTON | Title of Invention: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS |

**THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE-IDENTIFIED APPLICATION.**

1. Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee.
2. Check the box next to the appropriate selection:

   ☐ Each item of information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(1).

   **OR**

   ☑ No item of information contained in the IDS was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the IDS was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(2).

   **OR**

   ☐ See attached certification statement in compliance with 37 CFR 1.97(e).
3. Please charge the IDS fee set forth in 37 CFR 1.17(p) to Deposit Account No. 23-2415.
4. A Petition to Withdraw from Issue After Payment of the Issue Fee (37 CFR 1.313(c)(2)), including the petition fee set forth in 37 CFR 1.17(h), is submitted herewith as a **Web-based ePetition**. **WARNING:** Do not submit the petition as a follow-on paper via EFS-Web. Submit the petition as a Web-based ePetition by signing on to EFS-Web as a registered user, selecting the radio button next to "Existing application/patent," and then selecting the radio button next to "ePetition (for automatic processing and immediate grant, if all petitions requirements are met)." Failure to use the Web-based ePetition interface will result in automatic entry of the RCE.
5. A request for continued examination (RCE) under 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.
6. The RCE will be treated as a "conditional" RCE. In the event the examiner determines that any item of information contained in the IDS necessitates the reopening of prosecution in the application, the undersigned understands that (i) the RCE will be processed and treated as an RCE under 37 CFR 1.114 and therefore (ii) the IDS fee under 37 CFR 1.17(p) will be returned in accordance with 37 CFR 1.97(b)(4). In the event that no item of information in the IDS necessitates reopening prosecution, the undersigned understands that the RCE will not be processed and the RCE fee under 37 CFR 1.17(e) will be returned.
7. This certification and request is being filed as a **Web-based ePetition** and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE.

| Signature /Kaia R. Parenti/ | Date 2024-06-06 |
|---|---|
| Name (Print/Typed) Kaia R. Parenti | Practitioner Registration Number (If applicable) 81050 |

***Note:*** *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below.**

☐ *Total of _____ forms are submitted.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| 18/307,718 | 06/06/2024 04:32:24 PM Z ET | 50535-709.307 |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | 12005065 |
| CONFIRMATION # | 9067 | FILED BY | Kaia Parenti |
| PATENT CENTER # | 65861545 | AUTHORIZED BY | - |
| CUSTOMER # | 21971 | FILING DATE | 04/26/2023 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| DA / 232415 | E202466G33076556 | Kaia Parenti |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1464 | PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III) | 140.00 | 1 | 140.00 |
| 1801 | REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114) | 1360.00 | 1 | 1360.00 |
| | | | TOTAL AMOUNT: | $1,500.00 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2) with Assigned Patent Number)

| APPLICATION # | ATTORNEY DOCKET # | FILING DATE |
|---|---|---|
| 18307718 | 50535-709.307 | 04/26/2023 |

Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Application Information

| | | | |
|---|---|---|---|
| CONFIRMATION # | 9067 | FILING DATE | 04/26/2023 |
| ART UNIT | 1612 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| EXAMINER | CELESTE RONEY | | |

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

**A grantable petition requires the following items:**

(1) Petition fee; and
(2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination (Quick Path Information Disclosure Statement) - RCE request, submission, and fee are attached

## Applicant claims the following entity status

Regular Undiscounted

## Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:
An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

| Signature | Name | Registration # |
|---|---|---|
| /Kaia R. Parenti/ | Kaia Parenti | 81050 |

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

## NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | U.S. Serial No. 16/639,540 Office Action dated March 28, 2024. | ☐ |
| | 002 | U.S. Serial No. 18/078,649 Office Action dated March 21, 2024. | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2024-06-06 |
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

# United States Patent and Trademark Office

*Office of the Chief Financial Officer*

Document Code:WFEE

User :Terrance Lawrence

Sale Accounting Date:06/07/2024

| Sale Item Reference Number | Effective Date |
|---|---|
| 18307718 | 06/06/2024 |

| Document Number | Fee Code | Fee Code Description | Amount Paid | Payment Method |
|---|---|---|---|---|
| I202467H57377425 | 1806 | SUBMISSION- INFORMATION DISCLOSURE STMT | $260.00 | Deposit Account |

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

## NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | U.S. Serial No. 16/639,540 Office Action dated March 28, 2024. | ☐ |
| | 002 | U.S. Serial No. 18/078,649 Office Action dated March 21, 2024. | ☐ |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 06/13/2024 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2024-06-06 |
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

/CELESTE A RONEY/ 06/13/2024

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

21971 7590 06/20/2024
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| RONEY, CELESTE A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/20/2024 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

| **Corrected**<br>***Notice of Allowability*** | **Application No.**<br>18/307,718 | **Applicant(s)**<br>HOWERTON et al. | |
|---|---|---|---|
| | **Examiner**<br>CELESTE A RONEY | **Art Unit**<br>1612 | **AIA (FITF) Status**<br>Yes |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to IDS, filed 06/06/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-15 and 17-22 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All  b) ☐ Some*  c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 06/06/2024.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

# United States Patent and Trademark Office

*Office of the Chief Financial Officer*

Document Code:WFEE

User :Hieu Le

Sale Adjustment Accounting Date:06/25/2024

| Effective Date | Sale Accounting Date | Sale Item Reference Number |
|---|---|---|
| 06/25/2024 | 06/25/2024 | 18307718 |

| Document Number | Fee Code | Fee Code Description | Amount Paid | Payment Method |
|---|---|---|---|---|
| I20246OF28496345 | 1801 | RCE- 1ST REQUEST | $1,360.00 | DA |

# United States Patent and Trademark Office

*Office of the Chief Financial Officer*

Document Code:WFEE

User :Hieu Le

Refund Accounting Date:06/25/2024

| Effective Date | Sale Item Reference Number | Refund Total |
|---|---|---|
| 06/25/2024 | 18307718 | $1,360.00 |

| Document Number | Fee Code | Fee Code Description | Amount Paid | Payment Method | Account Number |
|---|---|---|---|---|---|
| I20246OF28496345 | 1801 | RCE- 1ST REQUEST | $1,360.00 | DA | 232415 |

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **07/11/2024 07:33:04 PM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Colleen Mensching |
| PATENT CENTER # | 66332578 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Victoria Cheng |

## Documents

**TOTAL DOCUMENTS: 1**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| Spruce 50535-709.307 - Internet Communications Authorization.pdf | 2 | Internet Communications Authorization | 610 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce 50535-709.307 - Internet Communications Authorization.pdf | FAC7930EEFE3596AF76CA9053D1668E976FFCDBA0510C6E3B45863523628521F2D170E2B39B0C268A25908DA728397049CC8F791290197EE6511AB8D47AA31BD |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

| AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS | | |
|---|---|---|
| | Application No. | 18/307,718 |
| | Filing Date | 04/26/2023 |
| | First Named Inventor | Alexis HOWERTON |
| | Art Unit | 1612 |
| | Examiner Name | Celeste A. RONEY |
| | Practitioner Docket No. | 50535-709.307 |

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**I. To authorize permission for Internet Communications.**

☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

**II. To withdraw authorization for Internet Communications.**

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 79641.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Victoria Cheng/ — Signature

July 11, 2024 — Date

Victoria Cheng — Typed or printed name

858/350-2240 — Telephone Number

**NOTE**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

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The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **07/12/2024 05:38:22 PM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Kaia Parenti |
| PATENT CENTER # | 66348141 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | - |

## Documents

**TOTAL DOCUMENTS: 13**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| petition-request.pdf | 2 | ePetition Request Form | 31 KB |
| NPL_NEUROCRINE_v_SPRUCE_DecisionGrantingPGR_USPN11007201_01Dec2023.pdf | 38 | Non Patent Literature | 3364 KB |
| NPL_DO_Copper-Catalyzed_Accession_390596_2008.pdf | 7 | Non Patent Literature | 2305 KB |
| FOR_WO2013160317A2.pdf | 120 | Foreign Reference | 4956 KB |
| NPL_US16639541_OA_4AP | 15 | Non Patent Literature | 532 KB |

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|---|---|---|---|---|
| RIL2022.pdf | | | | |
| FOR_WO2005020910A2.pdf | | 155 | Foreign Reference | 5014 KB |
| NPL_NEUROCRINE_v_SPRUCE_PetitionForPostGrantReview_USPN10849908_28May2021.pdf | | 90 | Non Patent Literature | 5422 KB |
| NPL_US17586228_OA_30MARCH2020.pdf | | 17 | Non Patent Literature | 588 KB |
| Spruce_50535-709.307_RCE.pdf | | 3 | Request for Continued Examination (RCE) | 1629 KB |
| FOR_CN101516835A_EFS.pdf | | 215 | Foreign Reference | 10155 KB |
| NPL_NEUROCRINE_v_SPRUCE_PetitionForPostGrantReview_USPN11007201_18Feb2022.pdf | | 92 | Non Patent Literature | 6033 KB |
| Spruce_50535-709_307_IDS_SB08_20240625_filingwithRCE_removingfromissue.pdf | | 8 | - | 98 KB |
| Spruce_50535-709_307_IDS_SB08_20240625_filingwithRCE_removingfromissue-TRAN.LET.pdf | (1-4) | 4 | Transmittal Letter | 38 KB |
| Spruce_50535-709_307_IDS_SB08_20240625_filingwithRCE_removingfromissue-IDS.pdf | (5-8) | 4 | Information Disclosure Statement (IDS) Form (SB08) | 55 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| petition-request.pdf | 15928964F5692A7B335CDB7418CA687F37068AC539CBECC0A389D045702B5A37B066F20A488A6C811B13852C1AE5F35C8BEE959DA3BD7DD1E2D4E9E705AFBA07 |
| NPL_NEUROCRINE_v_SPRUCE_DecisionGrantingPGR_USPN11007201_01Dec2023.pdf | FEE958B8E9ADCA3BA2055670284E8726B9018C741CD882B74FAD2D04B138C4556EF9215C63898B8316325A9D532A98971008B44440B64E26055CFD001029BB9 |
| NPL_DO_Copper-Catalyzed_Accession_390596_2008.pdf | 35A5588ECF2C4B4EAC7DFF155691DD9BB09E501F4FFE44E7FA24FC79E1CF508605A53C6A7E4FF227F1EEBEC92921B8BAE12C6265A3660C52C796259074B363A9 |
| FOR_WO2013160317A2.pdf | 78FEB2D63163C5AB983E7B5F512552F79389B34FB0B77C9F0D9E3DFECCAF8679D5882FAD05D832815590C600D9BA849157F5A8EDB75877A05F183253B0E0B97D |
| NPL_US16639541_OA_4APRIL2022.pdf | DA7EAFAAFF73D4B1BA7DEBA8A7BC8F24387C2067D21F8D1B25D2F0A97D8FD71D8D2BBE78F659B4171F12BF59FEF45AE40ECF1BA87288A2943A1EA310BE21C9B7 |
| FOR_WO2005020910A2.pdf | A92159558AAD22F4B8C8853C77AC20D2AFE2D703D6CA05B866CE8F1DB91892692B1AA5D6D090D30E47167C0A3E03C53FD89F5B3C7D72D73998CEF69584EB94CF |
| NPL_NEUROCRINE_v_SPRUCE_PetitionForPostGrantReview_USPN10849908_28May2021.pdf | 3619452D8081A5337814178A75D7A38DF1640100C1B1234C82C065E2FCADEFF6977BA7B50EB46A446AB76CC11E96A5CCE27681B45B532508F97D59A38433A056 |
| NPL_US17586228_OA_30MARCH2020.pdf | 6B5638BAF1D95DB3B8B865048ACC953EDBD3FF8A9A364BD938D6A6E0225B9E0383B19FE5AD00BDC8F16B401F95FD078822078068DE60C06C5C3B1B52AEE089CF |
| Spruce_50535-709.307_RCE.pdf | 6BCCF6E3FCCB8B6A0930BB6F2FA0E412CED8090938104EBAFE782952BDEEC019180C570E79FFE3B9D7D3D4DBCA6878F1 |

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| FOR_CN101516835A_EFS.pdf | 0E9A6BEE44EBA99D5150D1AB8DA053E8B37351F5BB1A12E5789BDB9AB840AB5C6A8DD6E88722BA1BA71563E026B6A40921B8279D53E682C33341E84769FB413D |
| NPL_NEUROCRINE_v_SPRUCE_PetitionForPostGrantReview_USPN11007201_18Feb2022.pdf | 7F585C92FE36BE5D2A92E2889BA548C11CAF1641F91832CF2B6194ABC1DB55A5064D1CEA3F57207D5A697E43F4BEA5F7EBC4C503C571C5A0EA9275485FA6A36A |
| Spruce_50535-709_307_IDS_SB08_20240625_filingwithRCE_removingfromissue.pdf | 42F23E2465131A2A69064D47E20A6D06492F852062B3BDCDF23446AAA3F9BF631F217B6933F51DF7B84A098C8CBE19F62730417785077D967EE3823D2485FC3E |
| Spruce_50535-709_307_IDS_SB08_20240625_filingwithRCE_removingfromissue-TRAN.LET.pdf | 633B43C55FEC7F3F84136D5FF44F9CCB202C58BB1946F8211BEA6F04D278C19F18E5E0D0A01D9B491AD38C247206C7711E4B6B31C9E14B86579C6AD91BBA29D8 |
| Spruce_50535-709_307_IDS_SB08_20240625_filingwithRCE_removingfromissue-IDS.pdf | 2FC56AFA56F4BCEB23A48FE574489C889059CE11A550F106EC494D445A7DE09161B71B94B649790507874A951F5038D036D35DA04AEA813165B2100542A38D4B |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

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PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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# REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
## (Submitted Only via EFS-Web)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application Number | 18/307,718 | Filing Date | 2023-04-26 | Docket Number (if applicable) | 50535-709.307 | Art Unit | 1612 |
| First Named Inventor | Alexis HOWERTON | | | Examiner Name | Celeste A. RONEY | | |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

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☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

### FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to
Deposit Account No 232415

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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| Signature of Registered U.S. Patent Practitioner | | | |
|---|---|---|---|
| Signature | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2024-07-12 |
| Name | Kaia R. Parenti | Registration Number | 81050 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is t file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Tim will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions f reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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31 October 2013 (31.10.2013)

WIPO | PCT

(10) International Publication Number
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(26) Publication Language: English

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(71) Applicant: **HOLSBOERMASCHMEYER NEUROCHEMIE GMBH** [DE/DE]; Maximilianstrasse 13, 80539 Munich (DE).

(72) Inventor: **HOLSBOER, Florian**; Rohmederstrasse 12, 80805 Munich (DE).

(74) Agent: **HUENGES, Martin**; Maiwald Patentanwalts GmbH, Postfach 33 05 23, 80065 Munich (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: CRHR1 ANTAGONISTS FOR USE IN THE TREATMENT OF PATIENTS HAVING CRH OVERACTIVITY

(57) **Abstract**: The present invention relates to a corticotropin releasing hormone receptor type 1 (CRHRl) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in a novel group of patients, i.e. patients having corticotropin releasing hormone (CRH) overactivity.

WO 2013/160317 A2

# CRHR1 antagonists for use in the treatment of patients having CRH overactivity

## Field of the Invention

The present invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

## Background of the Invention

While current antidepressant drugs are effective treatments of depression and anxiety symptoms in a number of psychiatric disorders, a large fraction of patients only show partial remission of symptoms or do not respond at all (Trivedi *et al.*, Am J Psychiatry, 2006). This may be due to the fact that these drugs do not target the inherent pathophysiologic disturbances leading to clinical condition in these patients. A number of novel antidepressant strategies, derived from both animal studies and human studies have been tested, but so far with little success. One of these approaches is the use of corticotropin releasing hormone receptor type 1 (CRHR1) antagonists. A wealth of data ranging from molecular studies in experimental animals to open label studies in human patients indicate that CRHR1 antagonists are a promising novel approach in the treatment of depression and anxiety (Ising *et al.*, Exp Clin Psychopharmacol, 2007; Holsboer *et al.*, CNS Spectr, 2001; Paez-Pereda *et al.*, Expert Opin Invest Drugs, 2011). However, so far all randomized clinical trials have failed to demonstrate the superiority of this drug to placebo (Coric *et al.*, Depress Anxiety, 2010; Binneman *et al.*, Am J Psychiatry, 2008).

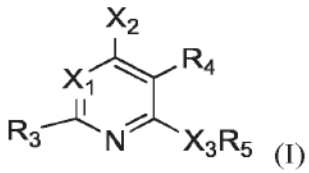
Hence, there is still a need for antidepressant drugs effective in the treatment of depression and/or anxiety symptoms in a number of psychiatric disorders.

It has now been found that despite the so far unsuccessful clinical trials, a specific group of patients, i.e. patients suffering from central corticotropin releasing hormone (CRH) overactivity, profits from the treatment with CRHR1 antagonists.

Summary of the Invention

One aspect of the invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

In an embodiment of the invention, the CRHR1 antagonist is a compound of formula (I)


(I)

or a pharmaceutically acceptable salt thereof, wherein

$X_1$ is $-CR_6$ or N;

$X_2$ is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

$X_3$ is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{11}R_{12})$, wherein $R_{11}$ and $R_{12}$ are each, independently, hydrogen, trifluoromethyl or methyl, or one of $R_{11}$ and $R_{12}$ is cyano and the other is hydrogen or methyl, or
$X_3$ is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$;

$R_1$ is $C_1\text{-}C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-O\text{-}CO\text{-}(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}NH(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}$

$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond;

$R_2$ is $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ alkoxyalkyl, aryl or -($C_1$-$C_4$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –($C_1$-$C_6$ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl;

and wherein each of the foregoing $R_2$ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl, or with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -$NR_1R_2$ or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

$R_3$ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, $OCF_3$, methylthio, methylsulfonyl, $CH_2OH$, or $CH_2OCH_3$;

$R_4$ is hydrogen, $C_1$-$C_4$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_4$ alkoxy, trifluoromethoxy, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH_2OCF_3$, $CF_3$,

amino, nitro, -NH($C_1$-$C_4$ alkyl), -N($CH_3$)$_2$, -NHCOCH$_3$ -NHCONHCH$_3$, -SO$_n$($C_1$-$C_4$ alkyl) wherein n is 0, 1 or 2, hydroxy, -CO($C_1$-$C_4$ alkyl), -CHO, cyano or -COO($C_1$-$C_4$ alkyl) wherein said $C_1$-$C_4$ alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH($C_1$-$C_2$ alkyl), -N($C_1$-$C_2$ alkyl)$_2$, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, chloro, cyano and nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups $R_5$ is substituted with from one to three substituents independently selected from fluoro, chloro, $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, ($C_1$-$C_6$ alkyl)O($C_1$-$C_6$)alkyl, -NHCH$_3$, -N($CH_3$)$_2$, -COOH, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), -SO$_2$NH($C_1$-$C_4$ alkyl), -SO$_2$N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -SO$_2$NH$_2$, -NHSO$_2$($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl) and SO$_2$($C_1$-$C_6$ alkyl), and wherein the $C_1$-$C_4$ alkyl and the $C_1$-$C_6$ alkyl moieties of the foregoing $R_5$ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

$R_6$ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O($C_1$-$C_4$ alkyl), -C(O)($C_1$-$C_4$ alkyl), -C(O)O($C_1$-$C_4$ alkyl), -OCF$_3$, CF$_3$, -CH$_2$OH, -CH$_2$OCH$_3$ or -CH$_2$OCH$_2$CH$_3$;

$R_9$ is hydrogen, hydroxy, fluoro, or methoxy;

$R_{10}$ is hydrogen or $C_1$-$C_4$ alkyl.

Further, CRHR1 antagonists of the invention encompass compounds of formula (I) as defined above, wherein $X_1$ is –$CR_6$. Optionally, in the CRHR1 antagonists of the invention $X_1$ is -$CR_6$, wherein $R_6$ is hydrogen.

In a further embodiment of the CRHR1 antagonists of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ of the compound of formula (I) as defined above is substituted with at least one substituent selected from $C_1$-$C_4$ alkyl or with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or $SO_2$ and one to four carbon atoms may optionally be replaced by nitrogen.

In a specific embodiment of the CRHR1 antagonists of the invention, $X_2$ of the compound of formula (I) as defined above is $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

Optionally, in the compounds of formula (I) as defined above $-NHCHR_1R_2$ is $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$,, $-NHCH(CH_2CH_2OCH_3)_2$ or $-NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, or $-NR_1R_2$ is $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$, or $-OCHR_1R_2$ is $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$.

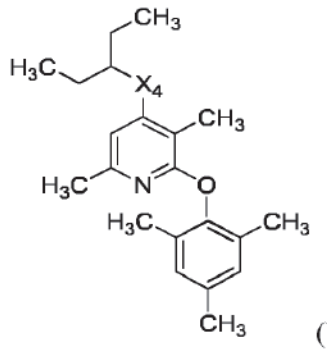
In another embodiment of the CRHR1 antagonists of the invention, $R_3$ and $R_4$ of the compound of formula (I) as defined above are methyl.

In a further embodiment of the CRHR1 antagonists of the invention, $X_3$ of the compound of formula (I) as defined above is O.

Another embodiment of the invention relates to the CRHR1 antagonists of formula (I) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituent(s) independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, $CF_3$.

A specific embodiment of the invention relates CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having

corticotropin releasing hormone (CRH) overactivity, wherein the CRHR1 antagonist is a compound of the formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
$X_4$ is O or NH.

In another specific embodiment, the CRHR1 antagonist of the invention is a class I or class II CRHR1 antagonist.

Another specific embodiment of the invention relates to a CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity, wherein the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965, SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is DMP-696.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is CP 316,311.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is SSR125543A.

Brief Description of the Drawings

**Figure 1:** Graph of the phenotypic distribution of ln(AAUC) at in-patient admission. The X-axis shows the ln of the AUC of the ACTH response and the Y-axis the frequency in total N/bin. The dashed vertical indicates the cut-off for being classified as a low vs. high responder. AAUC is the area under the curve of the ACTH response.

**Figure 2:** Increased REMS activity in CRH-COE$^{CNS}$ mice is suppressed by DMP696 (50mg/kg/d) application via drinking water. Treatment day one, light grey; treatment day 2, dark grey; treatment day three, black. Symbols indicate significant differences between baseline and treatment day one (+), two (#) or three (*). Light and dark bar on the x-axis indicate light and dark period, respectively.

**Figure 3:** Increased activity of REMS in CRH-COE$^{CNS}$ is suppressed by application of the CRH-R1 antagonist SSR125543 (50mg/kg/d) via drinking water. Baseline day, white; treatment day two, dark grey; treatment day three, black. Symbols indicate significant differences between baseline and treatment day two (#) or three (*). Light and dark bar on the x-axis indicate light and dark period, respectively.

**Figure 4:** REMS activity in Cor26 CRH mice is suppressed by application of the CRH-R1 antagonist CP-316311 (50mg/kg/d) via drinking water. Baseline day, white; treatment day two, dark grey; treatment day three, black.

Definitions

Where the term "comprise" or "comprising" is used in the present description and claims, it does not exclude other elements or steps. For the purpose of the present invention, the term "consisting of" is considered to be an optional embodiment of the

term "comprising of". If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also to be understood to disclose a group which optionally consists only of these embodiments.

Where an indefinite or a definite article is used when referring to a singular noun such as "a" or "an" or "the", this includes a plural form of that noun unless specifically stated. Vice versa, when the plural form of a noun is used it refers also to the singular form. For example, when SNPs are mentioned, this is also to be understood as a single SNP.

Furthermore, the terms first, second, third or (a), (b), (c) and the like in the description and in the claims are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

The term "corticotropin releasing hormone receptor 1" of "CRHR1" of "$CRF_1$" refers to the receptor which binds to corticotropin-releasing hormone.

The term "CRHR1 antagonist" refers to a compound capable of binding directly or indirectly to a CRH receptor 1 so as to modulate the receptor mediated activity. CRHR1 antagonists are well known in the literature and are e.g. described in WO 94/13676, EP 0 773 023, WO 2004/047866, WO 2004/094420, WO 98/03510, WO 97/029109, WO 2006/044958, WO 2001/005776 and WO 95/033750. Exemplary CRHR1 antagonists comprise NBI30775/R121919 (Neurocrine), CP316.311 (Pfizer), CP154,526 (Pfizer), Emicerfont (Glaxo), ONO-2333Ms (Ono Pharmaceutical), Pexacerfont (Bristol-Myers-Squibb), SSR125543 (Sanofi-Aventis), NBI-34101 (Neurocrine) and TAI041 (Taisho).

Most of the non-peptidic CRHR1 antagonists can be described by or adhere to a pharmacophore model that comprises or features a lipophilic top group, a

heterocyclic core containing an invariable hydrogen bond acceptor, which is almost always a heterocyclic nitrogen, and a lipophilic, usually aromatic, bottom group.

Class I CRHR1 antagonists as used herein may be characterized in that the heterocyclic hydrogen bond acceptor and the bottom group are connected by a two-atom linker as exemplified by CRHR1 antagonists R-121919, NBI-30545, CP-154526, DMP696, pexacerfont (BMS-562086), emicerfont (GW876008), or verucerfont (GSK561679). Class II CRF1R antagonists as used herein may be characterized by a two-atom linker between hydrogen bond acceptor and the bottom group as present in CRHR1 antagonist SSR125543A.

"Downstream target" or "molecule which is downstream of the CRHR1 receptor" as used herein may denote a molecule such as an endogenous molecule (e.g. peptide, protein, lipid, nucleic acid or oligonucleotide) that is regulated by CRHR1 directly or indirectly. The direct or indirect regulation may comprise direct or indirect modulation of the activity and/or expression level and/or localization, degradation, stability of the downstream target.

The term "normal CRH activity" refers to a range of CRH activity which can be found in human beings who are not affected by a condition which is associated with an increase of CRH activity (such as depression). A value indicative for normal CRH activity is usually considered to be indicative or predictive for a patient not responding to a treatment with a CRHR1 antagonist.

Further definitions of the terms will be given below in the context of which the terms are used.

Detailed Description of the Invention

While so far all randomized clinical trials have failed to demonstrate the superiority of CRHR1 antagonist to placebo in the treatment of depression and anxiety, it has now been found that a certain patient group, i.e. patients with corticotropin releasing

hormone (CRH) overactivity, is responsive to the treatment with corticotropin releasing hormone receptor type 1 (CRHR1) antagonists.

Hence, the present invention relates to CRHR1 antagonists for use in the treatment of depressive symptoms and/or anxiety symptoms in said novel patient group, i.e. patients having CRH overactivity.

The terms “CRH overactivity”, “CRH system overactivity”, “CRH hyperactivity”, “CRH hyperdrive” or "central CRH hyperdrive" are used herein interchangeable. An indication for CRH overactivity may be an increase in activity or concentration of CRH or of one or several molecules downstream of the CRHR1 receptor, that are activated or whose concentration is increased based on the activation of CRHR1 receptor upon CRH binding. A further indication for CRH overactivity may be a decrease in activity or concentration of one or several molecules downstream of the CRHR1 receptor, that are inactivated or whose concentration is decreased based on the activation of CRHR1 receptor upon CRH binding. A value indicative for CRH overactivity is usually considered to be indicative or predictive for a patient responding to a treatment with a CRHR1 antagonist. CRH activity vs. CRH overactivity may be defined relatively to the whole group, e.g. by using a median split of the area under the curve of the ACTH response in the dex/CRH test. Responses in the upper median may be categorized as being predictive of CRH overactivity, while responses in the lower median are indicative of normal CRH activity.

A “value indicative for CRH activity”, a "value indicative for CRH overactivity" and/or a "value indicative for normal CRH activity" can be obtained by determining the concentration or activity of CRH and/or of a downstream target of the CRHR1 receptor. The analysis is usually set up in a way that it can be excluded that the modulation of activity or concentration of a downstream target of the CRHR1 receptor is due to another disturbance than CRH activity. For instance, the concentrations or activities of adrenocorticotrophin (ACTH) and/or cortisol are useful biomarkers for determining a value indicative for CRH overactivity.

Typically, the CRH overactivity in each patient may be determined by measuring the ACTH and/or cortisol level response to a combined dexamethasone suppression/CRH stimulation test as described in Heuser *et al.* (J Psychiatr Res., 1994).

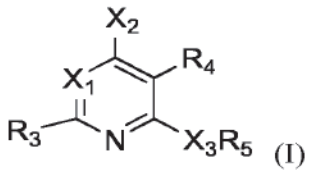
The neuroendocrine response to the dex/CRH test may be analyzed using the total area under the curve (AUC) of the ACTH response. Patients suffering from depression normally show an increased release of cortisol and of adrenocorticotropic hormone (ACTH) in response to the combined treatment with dexamethasone and CRH as performed during the test, thus indicating a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Patients with a high HPA axis dysregulation show AUC values of cortisol of between 3000 and 18000 AUC units (ng/ml x 75 min) and/or AUC values of ACTH of between 1000 and 6500 AUC units (pg/ml x 75 min). Patients having a low HPA axis dysregulation show AUC values of cortisol of between 300 and 2500 AUC units (ng/ml x 75 min) and/or AUC values of ACTH of between 250 and 1000 AUC units (pg/ml x 75 min) Various antidepressants lead to a reduction of these increased cortisol and ACTH levels in a combined dex/CRH test performed after the treatment with the antidepressants. Treatment response to antidepressants can thus be determined by performing a second dex/CRH test after treatment with the antidepressant and comparing the neuroendocrine response to the one shown in a combined dex/CRH test performed prior to treatment with the antidepressant.

In one embodiment of a combined dexamethasone suppression CRH stimulation test, subjects are pre-treated with dexamethasone and blood is drawn in certain intervals. Further, human CRH is administered after the first pretreatment with dexamethasone. Plasma ACTH and/or cortisol concentrations are then determined. The neuroendocrine response to the dex/CRH test may be analyzed using the total area under the curve (AUC) of the ACTH response. Details of an exemplary dex/CRH test are also described in Example 1 below.

Depressive symptoms comprise *inter alia* low mood, low self-esteem, loss of interest or pleasure, psychosis, poor concentration and memory, social isolation, psychomotor agitation/retardation, thoughts of death or suicide, significant weight change (loss/gain), fatigue, and feeling of worthlessness. The depressive disorders can last for weeks to lifelong disorder with periodic reoccurring depressive episodes. For the diagnosis of the depression mode (e.g. moderate or severe depression) the Hamilton Depression Rating Scale (HAM-D) (Hamilton, J Neurol Neurosurg Psychiatry, 1960) may be used. The depression mode may be also, in addition or alternatively, rated by alternative scales as the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Scale (MADRS), the Geriatric Depression Scale (GDS), and/or the Zung Self-Rating Depression Scale (ZSRDS).

Anxiety symptoms comprise *inter alia* panic disorders, generalized anxiety disorder, phobias and posttraumatic stress disorder. Typical symptoms of anxiety are or include avoidance behavior which may lead to social isolation, physical ailments like tachycardia, dizziness and sweating, mental apprehension, stress and/or tensions. The strength of these symptoms ranges from nervousness and discomfort to panic and terror in humans or animals. Most anxiety disorders may last for weeks or even months, some of them even for years and worsen if not suitably treated. For measuring the severity of anxiety symptoms, the Hamilton Anxiety Rating Scale (HAM-A) and/or the State-Trait Anxiety Rating Scale (STAI) can be used.

A CRHR1 antagonist which may be used according to the invention in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

$X_1$ is -$CR_6$ or N;

$X_2$ is -$NR_1R_2$, -$CR_1R_2R_9$, -$C(=CR_2R_{10})R_1$, -$NHCHR_1R_2$, -$OCHR_1R_2$, -$SCHR_1R_2$, -$CHR_2OR_{10}$, -$CHR_2SR_{10}$, -$C(S)R_2$ or -$C(O)R_2$;

$X_3$ is NH, O, S, -N($C_1$-$C_2$ alkyl) or -$C(R_{11}R_{12})$, wherein $R_{11}$ and $R_{12}$ are each, independently, hydrogen, trifluoromethyl or methyl, or one of $R_{11}$ and $R_{12}$ is cyano and the other is hydrogen or methyl, or

$X_3$ is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$;

$R_1$ is $C_1$-$C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond;

$R_2$ is $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ alkoxyalkyl, aryl or -($C_1$-$C_4$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –($C_1$-$C_6$ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl;

and wherein each of the foregoing $R_2$ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl, or with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$,

-SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -$NR_1R_2$ or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

$R_3$ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, $OCF_3$, methylthio, methylsulfonyl, $CH_2OH$, or $CH_2OCH_3$;

$R_4$ is hydrogen, $C_1$-$C_4$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_4$ alkoxy, trifluoromethoxy, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH_2OCF_3$, $CF_3$, amino, nitro, -NH($C_1$-$C_4$ alkyl), -$N(CH_3)_2$, -$NHCOCH_3$ -$NHCONHCH_3$, -$SO_n$($C_1$-$C_4$ alkyl) wherein n is 0, 1 or 2, hydroxy, -CO($C_1$-$C_4$ alkyl), -CHO, cyano or -COO($C_1$-$C_4$ alkyl) wherein said $C_1$-$C_4$ alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH($C_1$-$C_2$ alkyl), -N($C_1$-$C_2$ alkyl)$_2$, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, chloro, cyano and nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups $R_5$ is substituted with from one to three substituents independently selected from fluoro, chloro, $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, ($C_1$-$C_6$ alkyl)O($C_1$-$C_6$)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), -$SO_2$NH($C_1$-$C_4$ alkyl), -$SO_2$N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -$SO_2NH_2$, -$NHSO_2$($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl) and $SO_2$($C_1$-$C_6$ alkyl), and wherein the $C_1$-$C_4$ alkyl and the $C_1$-$C_6$ alkyl moieties of the foregoing $R_5$ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

$R_6$ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O($C_1$-$C_4$ alkyl), -C(O)($C_1$-$C_4$ alkyl), -C(O)O($C_1$-$C_4$ alkyl), -$OCF_3$, $CF_3$, -$CH_2OH$, -$CH_2OCH_3$ or -$CH_2OCH_2CH_3$;

$R_9$ is hydrogen, hydroxy, fluoro, or methoxy;

$R_{10}$ is hydrogen or $C_1$-$C_4$ alkyl.

In an embodiment of the invention, the CRHR1 antagonist of the present invention is a compound of formula (I) as defined above, wherein $X_1$ is –$CR_6$.

Alternatively, the CRHR1 antagonists of the invention encompass compound of formula (I) as defined above, wherein $X_1$ is N.

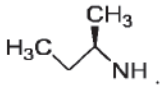
If $X_1$ is –$CR_6$, $R_6$ may be selected from the group consisting of hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O($C_1$-$C_4$ alkyl), -C(O)($C_1$-$C_4$ alkyl), -C(O)O($C_1$-$C_4$ alkyl), -$OCF_3$, $CF_3$, -$CH_2OH$, -$CH_2OCH_3$ or -$CH_2OCH_2CH_3$. In a specific embodiment of the CRHR1 antagonists of the invention $R_6$ is hydrogen.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (I) as defined above, wherein $X_2$ is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -$NR_1R_2$.

In a specific embodiment, $X_2$ is –$NHCHR_1R_2$. In another specific embodiment, $X_2$ is –$OCHR_1R_2$. In a further specific embodiment, $X_2$ is –$NR_1R_2$.

If $X_2$ is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, -$NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH_3)(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically $X_2$ is -$NHCH(CH_2CH_3)_2$. Alternatively, $X_2$ is -$NHCHR_1R_2$ wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl. Alternatively, $X_2$ is -$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, $X_2$ is –

$NHCH(CH_2OCH_3)_2$. Alternatively, $X_2$ is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, $X_2$ is



Alternatively, if $X_2$ is $-NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)$($CH_2$-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or-$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, $X_2$ is $-N(CH_2CH_2OCH_3)_2$.

If $X_2$ is -$OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, $X_2$ is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (I) as defined above wherein $R_1$ is $C_1$-$C_6$ alkyl.

In another embodiment of the invention, $R_1$ of formula (I) is $C_1$ alkyl. In a further embodiment of the invention $R_1$ of formula (I) is $C_2$ alkyl. In a further embodiment of the invention, $R_1$ of formula (I) is $C_3$ alkyl. In a further embodiment of the invention, $R_1$ of formula (I) is $C_4$ alkyl. In a further embodiment, of the invention, $R_1$ of formula (I) is $C_5$ alkyl. In a further embodiment of the invention, $R_1$ of formula (I) is $C_6$ alkyl.

Any of the aforementioned $R_1$ groups may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl). Said $C_1$-$C_6$ alkyl and the

($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond.

Specifically, $R_1$ is $C_1$-$C_6$ alkyl substituted with substituent $R_7$ selected from the group consisting of F, $CF_3$, $C_1$-$C_4$ alkoxy and $C_3$-$C_8$ cycloalkyl. More specifically, $R_1$ is selected from the group consisting of $-CH_2OCH_3$, $-CH_2CH_2OCH_3$ and $-CH_2$-cyclopropyl.

In another embodiment of the invention, $R_2$ of formula (I) is $C_1$-$C_{12}$ alkyl. In another embodiment of the invention, $R_2$ of formula (I) is $C_1$-$C_{12}$ alkoxyalkyl. In a further embodiment, $R_2$ is aryl. In another embodiment, $R_2$ is -($C_1$-$C_4$ alkylene)aryl. In a further embodiment of the invention, $R_2$ is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, $R_2$ is a –($C_1$-$C_6$ alkylene)cycloalkyl.

Optionally, if the $R_2$ group is aryl or –($C_1$-$C_4$ alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, $R_2$ is oxadiazolyl.

Optionally, if the $R_2$ group is a 3- to 8-membered cycloalkyl or a –($C_1$-$C_6$ alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl.

Each of the aforementioned $R_2$ groups may be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Alternatively, each of the aforementioned $R_2$ groups may be substituted with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and

-$SO_2$($C_1$-$C_4$ alkyl). Optionally, said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, $R_2$ is aryl substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Optionally, $R_2$ is aryl substituted with one substituent selected from chloro, fluoro and $C_1$-$C_4$ alkyl. More specifically, $R_2$ is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, $C_1$-$C_4$ alkyl, $CF_3$ and cyclopropyl. Even more specifically, $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is –$NHCHR_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, C1-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond and $R_2$ is oxadiazolyl substituted with methyl. Optionally, $X_2$ is –$NHCR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl.

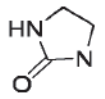
In another embodiment of the invention $X_2$ is -$NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention $X_2$ is –$CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -$NR_1R_2$ or –$CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

In a specific embodiment, -$NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur

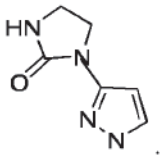
atom. Optionally, -$NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by –$NR_1R_2$ is a pyrazol-1-yl. Alternatively, -$NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by –$NR_1R_2$ or –$CR_1R_2R_9$ may be substituted with at least one substituent. In one embodiment of the invention, the 5- to 8-membered ring formed by –$NR_1R_2$ or –$CR_1R_2R_9$ is substituted with one substituent selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by –$NR_1R_2$ or –$CR_1R_2R_9$ is substituted with two substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by –$NR_1R_2$ or –$CR_1R_2R_9$ is substituted with three substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by –$NR_1R_2$ or –$CR_1R_2R_9$ is substituted with four substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by $SO_2$. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by $SO_2$. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by –$NR_1R_2$ is substituted with



Optionally, $X_2$ is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5 membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, $X_2$ is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one $C_1$-$C_4$ alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two $C_1$-$C_4$ alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with three $C_1$-$C_4$ alkyl substituents. Optionally, $X_2$ is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

A further embodiment of the invention encompasses CRHR1 antagonists of formula (I) as defined above, wherein $X_3$ is NH, O, $NCH_3$, or N, whereby, if $X_3$ is N, $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$. Specifically, $X_3$ of formula (I) as defined above is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with

$R_5$. More specifically, $X_3$ of formula (I) as defined above is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$ wherein $X_3$ and $R_4$ form a group –N-$CH_2CH_2$-. Alternatively, $X_3$ is O or NH, more specifically $X_3$ is O.

The CRHR1 antagonist of the invention further encompasses a compound of formula (I) as defined above, wherein $R_3$ is methyl. In a further embodiment of the invention, $R_4$ of formula (I) as defined above is $C_1$-$C_4$ alkyl. Optionally $R_4$ of formula (I) as defined above is methyl. Alternatively, $R_4$ of formula (I) as defined above is ethyl. The present invention also encompasses CRHR1 antagonists wherein both $R_3$ and $R_4$ are methyl.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (I) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, ($C_1$-$C_6$ alkyl)O($C_1$-$C_6$)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), -$SO_2$NH($C_1$-$C_4$ alkyl), -$SO_2$N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -$SO_2NH_2$, -$NHSO_2$($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl) and $SO_2$($C_1$-$C_6$ alkyl). The $C_1$-$C_4$ alkyl and the $C_1$-$C_6$ alkyl moieties of the foregoing $R_5$ groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituent(s) independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$. In a specific embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein $R_5$ is phenyl substituted with one substituent independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein $R_5$ is phenyl substituted with two substituents independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, $CF_3$. In another embodiment of the invention,

the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein $R_5$ is phenyl substituted with three substituents independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$.

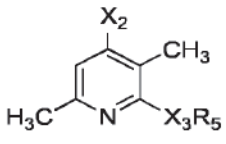
In a specific embodiment of the CRHR1 antagonist of the invention, $R_5$ is phenyl substituted with two substituents, wherein the two substituents are $CH_3$ and $OCH_3$.

In another specific embodiment of the CRHR1 antagonist of the invention, $R_5$ is phenyl substituted with three substituents, wherein the three substituents are $CH_3$.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from $CH_3$ and Cl.

Specifically, $R_5$ is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl, or 2,4-dimethoxy-phenyl. More specifically $R_5$ is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, $R_5$ is 4-chloro-2,6-dimethyl-phenyl.

In a specific embodiment of the invention, the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (II)



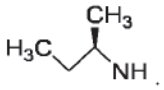
(II),

wherein $X_2$, $X_3$, $R_1$, $R_2$ und $R_5$-$R_{12}$ are as defined above for formula (I).

A further embodiment of the invention relates to a CRHR1 antagonist of formula (II) as defined above, wherein $X_2$ is selected from the group consisting of $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, $X_2$ is $-NHCHR_1R_2$. In another specific embodiment, $X_2$ is $-OCHR_1R_2$. In a further specific embodiment, $X_2$ is $-NR_1R_2$.

If $X_2$ is $-NHCHR_1R_2$, it is optionally selected from the group consisting of $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, $X_2$ is $-NHCH(CH_2CH_3)_2$. Alternatively, $X_2$ is $-NHCHR_1R_2$ wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl. Alternatively, $X_2$ is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, $X_2$ is $-NHCH(CH_2OCH_3)_2$. Alternatively, $X_2$ is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, $X_2$ is



Alternatively, if $X_2$ is $-NR_1R_2$, it is optionally selected from the group consisting of $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, $X_2$ is $-N(CH_2CH_2OCH_3)_2$.

If $X_2$ is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, $X_2$ is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (II) as defined above wherein $R_1$ is $C_1$-$C_6$ alkyl.

In another embodiment of the invention, $R_1$ of formula (II) is a $C_1$ alkyl. In a further embodiment of the invention, $R_1$ of formula (II) is a $C_2$ alkyl. In a further embodiment of the invention, $R_1$ of formula (II) is a $C_3$ alkyl. In a further embodiment of the invention, $R_1$ of formula (II) is a $C_4$ alkyl. In a further embodiment of the invention, $R_1$ of formula (II) is a $C_5$ alkyl. In a further embodiment of the invention, $R_1$ of formula (II) is a $C_6$ alkyl.

Any of the aforementioned $R_1$ groups may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, C1-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl). Said $C_1$-$C_6$ alkyl and/or the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond.

Specifically, $R_1$ is $C_1$-$C_6$ alkyl substituted with substituent $R_7$ selected from the group consisting of F, $CF_3$, $C_1$-$C_4$ alkoxy and $C_3$-$C_8$ cycloalkyl. More specifically, $R_1$ is selected from the group consisting of –$CH_2OCH_3$, -$CH_2CH_2OCH_3$ and –$CH_2$-cyclopropyl.

In another embodiment of the invention, $R_2$ of formula (II) is $C_1$-$C_{12}$ alkyl. In another embodiment of the invention, $R_2$ of formula (II) is $C_1$-$C_{12}$ alkoxyalkyl. In a further embodiment, $R_2$ is aryl. In another embodiment, $R_2$ is -($C_1$-$C_4$ alkylene)aryl. In a further embodiment of the invention, $R_2$ is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, $R_2$ is a –($C_1$-$C_6$ alkylene)cycloalkyl.

Optionally, if the $R_2$ group is aryl or –($C_1$-$C_4$ alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl,

benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, $R_2$ is oxadiazolyl.

Optionally, if the $R_2$ group is a 3- to 8-membered cycloalkyl or a –($C_1$-$C_6$ alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl.

Each of the aforementioned $R_2$ groups may be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Alternatively, each of the aforementioned $R_2$ groups may be substituted with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl). Optionally, said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, $R_2$ is aryl substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Optionally, $R_2$ is aryl substituted with one substituent selected from chloro, fluoro and $C_1$-$C_4$ alkyl. More specifically, $R_2$ is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, $C_1$-$C_4$ alkyl, $CF_3$ and cyclopropyl. Even more specifically, $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is –NHCH$R_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and the ($C_1$-

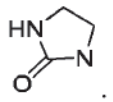
$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond and $R_2$ is oxadiazolyl substituted with methyl. Optionally, $X_2$ is $-NHCR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is $-NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, $X_2$ is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

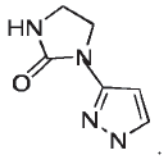
In a specific embodiment, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from $C_1$-$C_4$ alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by $SO_2$. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by $SO_2$. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



Optionally, $X_2$ is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, $X_2$ is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one $C_1$-$C_4$ alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two $C_1$-$C_4$ alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three $C_1$-$C_4$ alkyl substituents. Optionally, $X_2$ is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

A further embodiment of the invention encompasses CRHR1 antagonists of formula (II) as defined above, wherein $X_3$ is NH, O, $NCH_3$, or N, whereby if $X_3$ is N, $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$. Specifically, $X_3$ of formula (II) as defined above is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$. More specifically, $X_3$ of formula (II) as defined above is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$, wherein $X_3$ and $R_4$ form a group $-N\text{-}CH_2CH_2-$. Alternatively, $X_3$ is O or NH, more specifically $X_3$ is O.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (II) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, ($C_1$-$C_6$ alkyl)O($C_1$-$C_6$)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), $-SO_2NH$($C_1$-$C_4$ alkyl), $-SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), $-SO_2NH_2$, $-NHSO_2$($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl) and $SO_2$($C_1$-$C_6$ alkyl). The $C_1$-$C_4$ alkyl and the $C_1$-$C_6$ alkyl moieties of the foregoing $R_5$ groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituent(s) independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl,

F, $CF_3$. In a specific embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein $R_5$ is phenyl substituted with one substituent independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, $CF_3$. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein $R_5$ is phenyl substituted with two substituents independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, $CF_3$. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein $R_5$ is phenyl substituted with three substituents independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, $CF_3$.

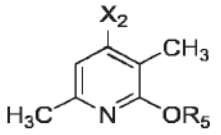
In a specific embodiment of the CRHR1 antagonist of the invention, $R_5$ is phenyl substituted with two substituents, wherein the two substituents are $CH_3$ and $OCH_3$.

In another specific embodiment of the CRHR1 antagonist of the invention, $R_5$ is phenyl substituted with three substituents, wherein the three substituents are $CH_3$.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from $CH_3$ and Cl.

Specifically, $R_5$ is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl, or 2,4-dimethoxy-phenyl. More specifically $R_5$ is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, $R_5$ is 4-chloro-2,6-dimethyl-phenyl.

In another specific embodiment of the invention the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (III)

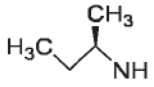

(III),

wherein $X_2$, $R_1$, $R_2$ und $R_5$-$R_{10}$ are as defined for formulas (I) and (II) above.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (III) as defined above, wherein $X_2$ is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -$NR_1R_2$.

In a specific embodiment, $X_2$ is –$NHCHR_1R_2$. In another specific embodiment, $X_2$ is –$OCHR_1R_2$. In a further specific embodiment, $X_2$ is –$NR_1R_2$.

If $X_2$ is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, -$NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH_3)(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, $X_2$ is -$NHCH(CH_2CH_3)_2$. Alternatively, $X_2$ is -$NHCHR_1R_2$ wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl. Alternatively, $X_2$ is –$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, $X_2$ is –$NHCH(CH_2OCH_3)_2$. Alternatively, $X_2$ is –$NHCH(CH_3)(CH_2CH_3)$. More specifically, $X_2$ is



Alternatively, if $X_2$ is –$NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or -$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. More specifically, $X_2$ is –$N(CH_2OCH_3)_2$. Alternatively, $X_2$ is -$N(CH_2CH_2OCH_3)_2$.

If $X_2$ is -$OCHR_1R_2$, it is optionally selected from –$OCH(CH_2CH_3)_2$, –$OCH(CH_2CH_3)CH_3$, –$OCH(CH_2CH_3)(CH_2CH_2CH_3)$, or –$OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, $X_2$ is –$OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention may encompass compounds of formula (III) as defined above wherein $R_1$ is $C_1$-$C_6$ alkyl.

In another embodiment of the invention, $R_1$ of formula (III) is a $C_1$ alkyl. In a further embodiment of the invention, $R_1$ of formula (III) is a $C_2$ alkyl. In a further embodiment of the invention, $R_1$ of formula (III) is a $C_3$ alkyl. In a further embodiment of the invention, $R_1$ of formula (III) is a $C_4$ alkyl. In a further embodiment of the invention, $R_1$ of formula (III) is a $C_5$ alkyl. In a further embodiment of the invention, $R_1$ of formula (III) is a $C_6$ alkyl.

Any of the aforementioned $R_1$ groups may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl). Said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond.

Specifically, $R_1$ is $C_1$-$C_6$ alkyl substituted with substituent $R_7$ selected from the group consisting of F, $CF_3$, $C_1$-$C_4$ alkoxy and $C_3$-$C_8$ cycloalkyl. More specifically, $R_1$ is selected from the group consisting of –$CH_2OCH_3$, -$CH_2CH_2OCH_3$ and –$CH_2$-cyclopropyl.

In another embodiment of the invention, $R_2$ of formula (III) is $C_1$-$C_{12}$ alkyl. In another embodiment of the invention, $R_2$ of formula (III) is $C_1$-$C_{12}$ alkoxyalkyl. In a further embodiment, $R_2$ is aryl. In another embodiment, $R_2$ is -($C_1$-$C_4$ alkylene)aryl.

In a further embodiment of the invention, $R_2$ is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, $R_2$ is a –($C_1$-$C_6$ alkylene)cycloalkyl.

Optionally, if the $R_2$ group is aryl or –($C_1$-$C_4$ alkylene)alkyl, said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, $R_2$ is oxadiazolyl.

Optionally, if the $R_2$ group is a 3- to 8-membered cycloalkyl or a –($C_1$-$C_6$ alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl.

Each of the aforementioned $R_2$ groups may be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Alternatively, each of the aforementioned $R_2$ groups may be substituted with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl). Optionally, said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, $R_2$ is aryl substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Optionally, $R_2$ is aryl substituted with one substituent selected from chloro, fluoro and $C_1$-$C_4$ alkyl. More specifically, $R_2$ is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, $C_1$-$C_4$ alkyl, $CF_3$ and cyclopropyl. Even more specifically, $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is –NHCH$R_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$

independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond and $R_2$ is oxadiazolyl substituted with methyl. Optionally, $X_2$ is –NHC$R_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is -N$R_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, $X_2$ is –C$R_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -N$R_1R_2$ or –C$R_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

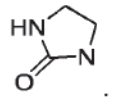
In a specific embodiment, -N$R_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, -N$R_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by –N$R_1R_2$ is a pyrazol-1-yl. Alternatively, -N$R_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by –N$R_1R_2$ or –C$R_1R_2R_9$ may be substituted with at least one substituent selected from $C_1$-$C_4$ alkyl or with a 4-8 membered ring.

In one embodiment of the invention, the 5- to 8-membered ring formed by –N$R_1R_2$ or –C$R_1R_2R_9$ is substituted with one substituent selected from $C_1$-$C_4$ alkyl or a 4-8

membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by $SO_2$. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by $SO_2$. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



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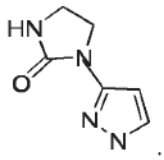
Optionally, $X_2$ is



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In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one

carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, $X_2$ is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the ring carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one $C_1$-$C_4$ alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two $C_1$-$C_4$ alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with three $C_1$-$C_4$ alkyl substituents. Optionally, $X_2$ is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (III) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, ($C_1$-$C_6$ alkyl)O($C_1$-$C_6$)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), $-SO_2NH$($C_1$-$C_4$ alkyl), $-SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), $-SO_2NH_2$, $-NHSO_2$($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl) and $SO_2$($C_1$-$C_6$ alkyl). The $C_1$-$C_4$ alkyl and the $C_1$-$C_6$ alkyl moieties of the foregoing $R_5$ groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein $R_5$ is phenyl substituted with from one to three substituent(s) independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$. In a specific embodiment of the invention, the CRHR1 antagonist

encompasses a compound of formula (III) as defined above, wherein $R_5$ is phenyl substituted with one substituent independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein $R_5$ is phenyl substituted with two substituents independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein $R_5$ is phenyl substituted with three substituents independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, and $CF_3$.

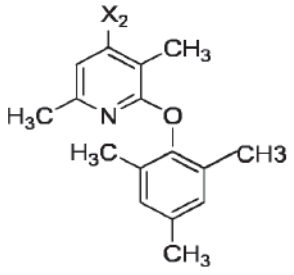
In a specific embodiment of the CRHR1 antagonist of the invention, $R_5$ is phenyl substituted with two substituents, wherein the two substituents are $CH_3$ and $OCH_3$.

In another specific embodiment of the CRHR1 antagonist of the invention, $R_5$ is phenyl substituted with three substituents, wherein the three substituents are $CH_3$.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from $CH_3$ and Cl.

Specifically, $R_5$ is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl or, 2,4-dimethoxy-phenyl. More specifically, $R_5$ is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, $R_5$ is 4-chloro-2,6-dimethyl-phenyl.

Another specific embodiment of the invention relates to a CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity, wherein the CRHR1 antagonist is a compound of formula (IV)



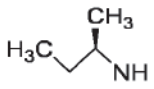

(IV),

wherein $X_2$, $R_1$, $R_2$, $R_7$, $R_8$, $R_9$ and $R_{10}$ are as defined above for formulas (I) to (III).

A further embodiment of the invention relates to a CRHR1 antagonist of formula (IV) as defined above, wherein $X_2$ is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -$NR_1R_2$.

In a specific embodiment, $X_2$ is –$NHCHR_1R_2$. In another specific embodiment, $X_2$ is –$OCHR_1R_2$. In a further specific embodiment, $X_2$ is –$NR_1R_2$.

If $X_2$ is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, $NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH)_3(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, $X_2$ is -$NHCH(CH_2CH_3)_2$. Alternatively, $X_2$ is -$NHCHR_1R_2$ wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl. Alternatively, $X_2$ is -$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, $X_2$ is -$NHCH(CH_2OCH_3)_2$. Alternatively, $X_2$ is –$NHCH(CH_3)(CH_2CH_3)$. More specifically, $X_2$ is




Alternatively, if $X_2$ is –$NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -

$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, $X_2$ is $-N(CH_2CH_2OCH_3)_2$.

If $X_2$ is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$ or $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, $X_2$ is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (IV) as defined above wherein $R_1$ is $C_1$-$C_6$ alkyl.

In another embodiment of the invention, $R_1$ of formula (IV) is a $C_1$ alkyl. In a further embodiment of the invention, $R_1$ of formula (IV) is a $C_2$ alkyl. In a further embodiment of the invention, $R_1$ of formula (IV) is a $C_3$ alkyl. In a further embodiment of the invention, $R_1$ of formula (IV) is a $C_4$ alkyl. In a further embodiment of the invention, $R_1$ of formula (IV) is a $C_5$ alkyl. In a further embodiment of the invention, $R_1$ of formula (IV) is a $C_6$ alkyl.

Any of the aforementioned $R_1$ groups may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and $-SO_2$($C_1$-$C_4$ alkyl). Said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond.

Specifically, $R_1$ is $C_1$-$C_6$ alkyl substituted with substituent $R_7$ selected from the group consisting of F, $CF_3$, $C_1$-$C_4$ alkoxy and $C_3$-$C_8$ cycloalkyl. More specifically, $R_1$ is selected from the group consisting of $-CH_2OCH_3$, $-CH_2CH_2OCH_3$ and $-CH_2$-cyclopropyl.

In another embodiment of the invention, $R_2$ of formula (IV) is $C_1$-$C_{12}$ alkyl. In another embodiment of the invention, $R_2$ of formula (IV) is $C_1$-$C_{12}$ alkoxyalkyl. In a further embodiment, $R_2$ is aryl. In another embodiment, $R_2$ is -($C_1$-$C_4$ alkylene)aryl. In a further embodiment of the invention, $R_2$ is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, $R_2$ is a –($C_1$-$C_6$ alkylene)cycloalkyl.

Optionally, if the $R_2$ group is aryl or –($C_1$-$C_4$ alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, $R_2$ is oxadiazolyl.

Optionally, if the $R_2$ group is a 3- to 8-membered cycloalkyl or a –($C_1$-$C_6$ alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl.

Each of the aforementioned $R_2$ groups may be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Alternatively, each of the aforementioned $R_2$ groups may be substituted with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl). Optionally, said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, $R_2$ is aryl substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Optionally, $R_2$ is aryl substituted with one substituent selected from chloro, fluoro and $C_1$-$C_4$ alkyl. More specifically, $R_2$ is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, $C_1$-$C_4$ alkyl, $CF_3$ and cyclopropyl. Even more specifically, $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is $-NHCHR_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and/or the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond and $R_2$ is oxadiazolyl substituted with methyl. Optionally, $X_2$ is $-NHCR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl.

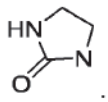
In another embodiment of the invention, $X_2$ is -$NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, $X_2$ is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -$NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

In a specific embodiment, -$NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, -$NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, -$NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the ring carbons is replaced by a sulfur atom.

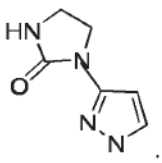
The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from $C_1$-$C_4$ alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring

formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by $SO_2$. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by $SO_2$. In a specific embodiment of the invention the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with




Optionally, $X_2$ is

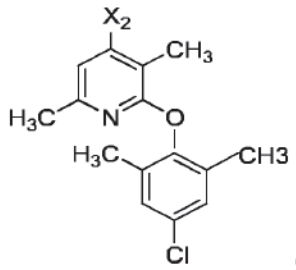



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally,

one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, $X_2$ is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$,containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one $C_1$-$C_4$ alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two $C_1$-$C_4$ alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$,containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three $C_1$-$C_4$ alkyl substituents. Optionally, $X_2$ is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

In another specific embodiment of the invention, the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (V)



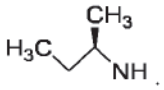

(V)

or a pharmaceutically acceptable salt thereof, wherein $X_2$, $R_1$, $R_2$, $R_7$, $R_8$, $R_9$ and $R_{10}$ are as defined for formulas (I)-(IV) above.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (V) as defined above, wherein $X_2$ is selected from the group consisting of $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, $X_2$ is $-NHCHR_1R_2$. In another specific embodiment, $X_2$ is $-OCHR_1R_2$. In a further specific embodiment, $X_2$ is $-NR_1R_2$.

If $X_2$ is $-NHCHR_1R_2$, it is optionally selected from the group consisting of $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$ wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, $X_2$ is $-NHCH(CH_2CH_3)_2$. Alternatively, $X_2$ is $-NHCHR_1R_2$ wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl. Alternatively, $X_2$ is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, $X_2$ is $-NHCH(CH_2OCH_3)_2$. Alternatively, $X_2$ is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, $X_2$ is



Alternatively, if $X_2$ is $-NR_1R_2$, it is optionally selected from the group consisting of $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, $X_2$ is $-N(CH_2CH_2OCH_3)_2$.

If $X_2$ is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$ or $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, $X_2$ is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (V) as defined above wherein $R_1$ is $C_1$-$C_6$ alkyl.

In another embodiment of the invention, $R_1$ of formula (V) is a $C_1$ alkyl. In a further embodiment of the invention, $R_1$ of formula (V) is a $C_2$ alkyl. In a further embodiment of the invention, $R_1$ of formula (V) is a $C_3$ alkyl. In a further embodiment of the invention, $R_1$ of formula (V) is a $C_4$ alkyl. In a further embodiment of the invention, $R_1$ of formula (V) is a $C_5$ alkyl. In a further embodiment of the invention, $R_1$ of formula (V) is a $C_6$ alkyl.

Any of the aforementioned $R_1$ groups may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl). Said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond.

Specifically, $R_1$ is $C_1$-$C_6$ alkyl substituted with substituent $R_7$ selected from the group consisting of F, $CF_3$, $C_1$-$C_4$ alkoxy and $C_3$-$C_8$ cycloalkyl. More specifically, $R_1$ is selected from the group consisting of –$CH_2OCH_3$, -$CH_2CH_2OCH_3$ and –$CH_2$-cyclopropyl.

In another embodiment of the invention, $R_2$ of formula (V) is $C_1$-$C_{12}$ alkyl. In another embodiment of the invention, $R_2$ of formula (V) is $C_1$-$C_{12}$ alkoxyalkyl. In a further embodiment, $R_2$ is aryl. In another embodiment, $R_2$ is -($C_1$-$C_4$ alkylene)aryl. In a further embodiment of the invention, $R_2$ is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, $R_2$ is a –($C_1$-$C_6$ alkylene)cycloalkyl.

Optionally, if the $R_2$ group is aryl or –($C_1$-$C_4$ alkylene)alkyl, said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl,

benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, $R_2$ is oxadiazolyl.

Optionally, if the $R_2$ group is a 3- to 8-membered cycloalkyl or a –($C_1$-$C_6$ alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl.

Each of the aforementioned $R_2$ groups may be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Alternatively each of the aforementioned $R_2$ groups may be substituted with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl). Optionally, said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, $R_2$ is aryl substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl. Optionally, $R_2$ is aryl substituted with one substituent selected from chloro, fluoro and $C_1$-$C_4$ alkyl. More specifically, $R_2$ is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, $C_1$-$C_4$ alkyl, $CF_3$ and cyclopropyl. Even more specifically, $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is –NHCH$R_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl), -COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl) and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_6$ alkyl and/or the

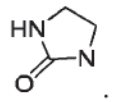
($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond and $R_2$ is oxadiazolyl substituted with methyl. Optionally, $X_2$ is $-NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl.

In another embodiment of the invention, $X_2$ is $-NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, $X_2$ is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

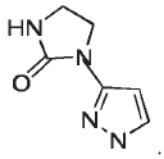
In a specific embodiment, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from $C_1$-$C_4$ alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from $C_1$-$C_4$ alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by $SO_2$. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by $SO_2$. In a specific embodiment of the invention the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



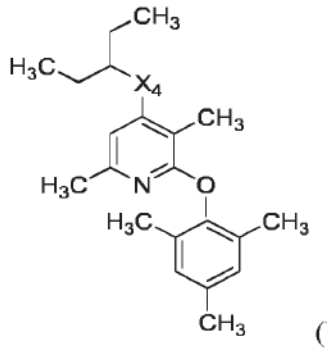
Optionally, $X_2$ is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5 membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, $X_2$ is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with at least one $C_1$-$C_4$ alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with two $C_1$-$C_4$ alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three $C_1$-$C_4$ alkyl substituents. Optionally, $X_2$ is 3,5-Dialkylpyrazol-1-yl, more specifically 3,5-Diethylpyrazol-1-yl.

In another specific embodiment of the invention the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
$X_4$ is O or NH.

In another embodiment of the invention, the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965, SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

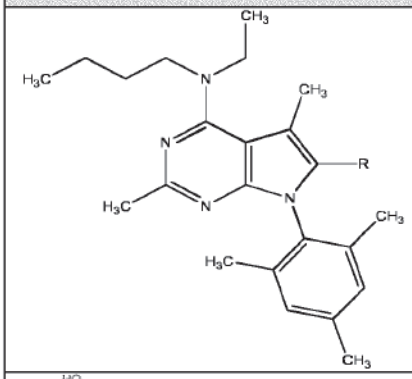
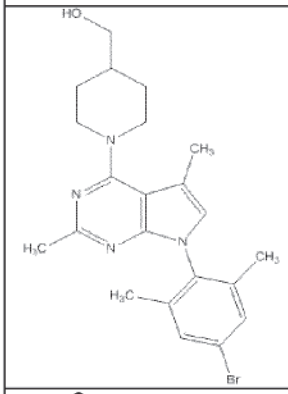
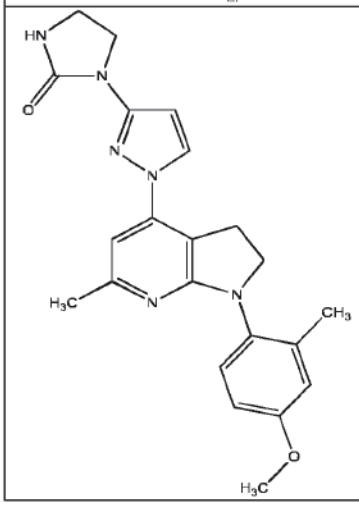
In a particular embodiment of the invention, the CRHR1 antagonist is DMP-696.

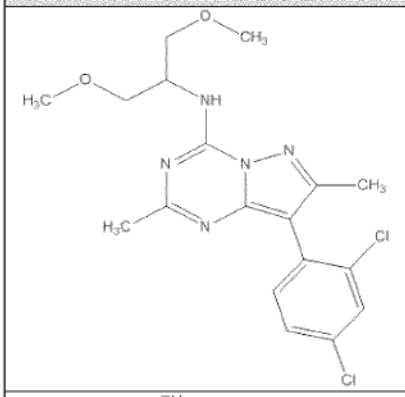
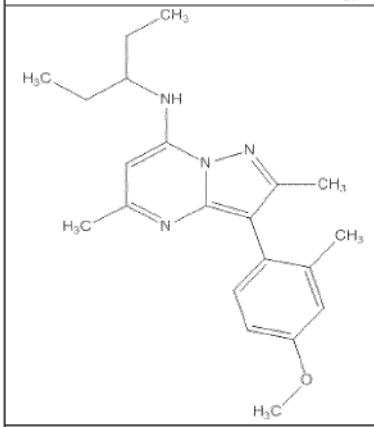
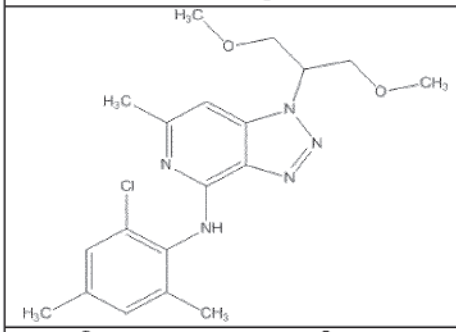
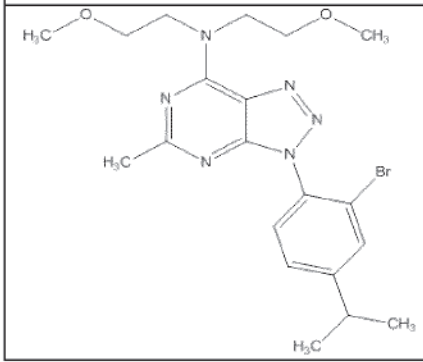
In a particular embodiment of the invention, the CRHR1 antagonist is CP-316,311.

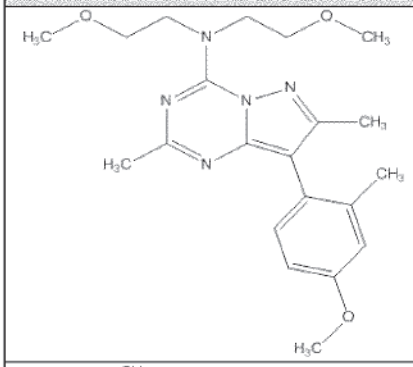
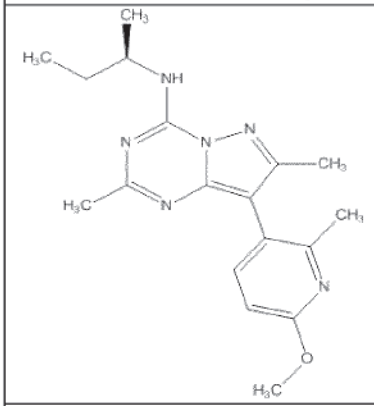
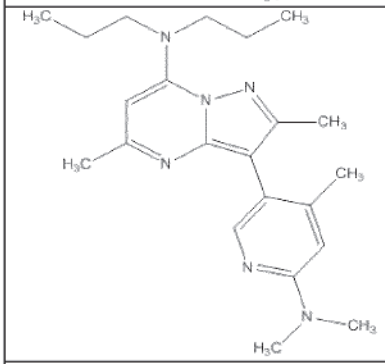
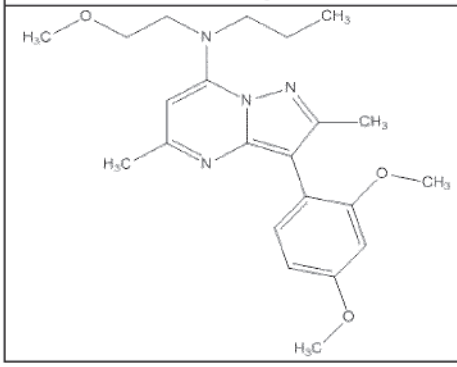
In a particular embodiment of the invention, the CRHR1 antagonist is SSR125543A

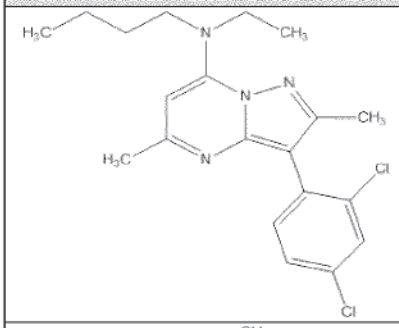
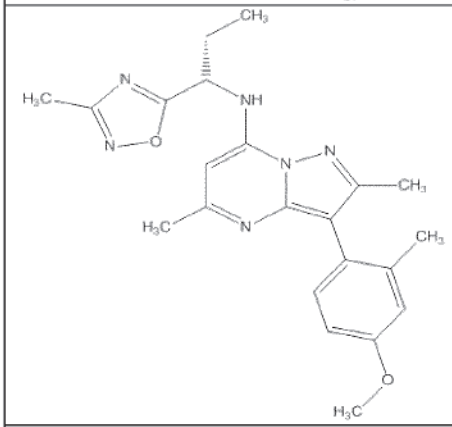
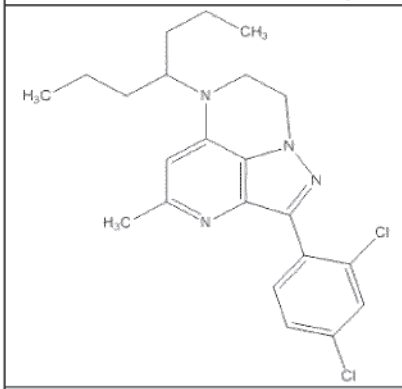
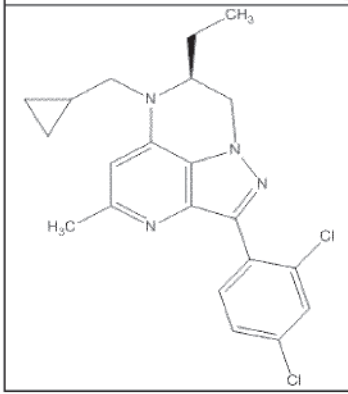
The corresponding structural formulas of some of the above-mentioned CRHR1 antagonists for use in the present invention are set out in Table 1 below:

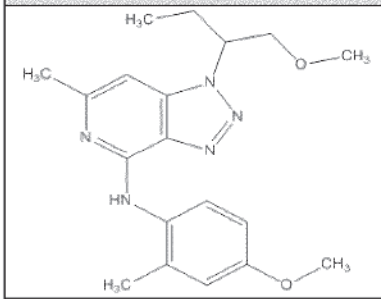
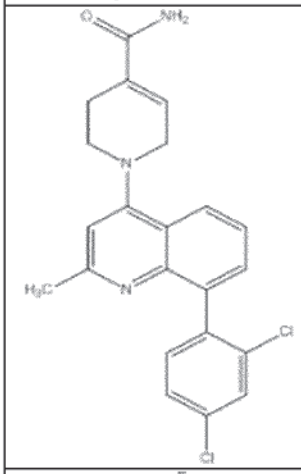
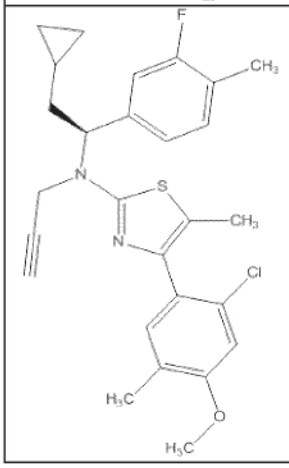
**Table 1**

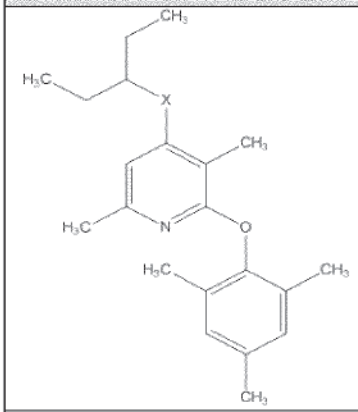
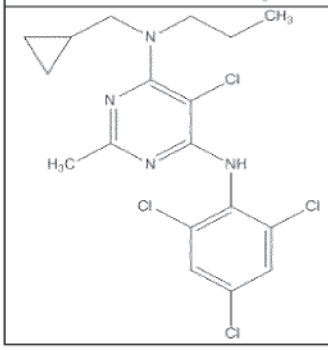
| Structural formula | CRHR1 antagonist (name) |
|---|---|
|  | R = H **CP154,526**<br>R = $CH_3$ **Antalarmin** |
|  | **CRA5626 / R317573 / JNJ19567470 / TAI-041** |
|  | **GW876008 /Emicerfont** |

| Structural formula | CRHR1 antagonist (name) |
|---|---|
|  | DMP-696 |
|  | DMP-904 |
|  | DMP-695 |
|  | SC-241 / LWH-234 |

| Structural formula | CRHR1 antagonist (name) |
|---|---|
|  | BMS-561388 |
|  | BMS-562086 / Pexacerfont |
|  | R121919 / NBI30775 |
|  | NBI30545 |

| Structural formula | CRHR1 antagonist (name) |
|---|---|
|  | **PD-171729** |
|  | **GSK561679 / NBI-77860 / Verucerfont** |
|  | **SB-723620 / NBI34041** |
|  | **NBI35965** |

| Structural formula | CRHR1 antagonist (name) |
|---|---|
|  | **SN003** |
|  | **CRA0450 / R278995** |
|  | **SSR125543A** |

| Structural formula | CRHR1 antagonist (name) |
|---|---|
|  | X = O **CP-316,311**<br>X = NH **CP-376,395** |
|  | **NBI-27914** |

ONO-2333Ms, NBI 34101, PF-572778, GSK561579 and GSK586529 are described by Zorilla and Koob (Drug Discovery Today, 2010, 371-383) as corticotropin releasing factor receptor antagonists (corticotropin releasing factor is a synonym for CRHR1 antagonists) tested in clinical trials.

In another aspect of the invention, the above-described CRHR1 antagonists are for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity, wherein CRH overactivity is detected by determining the status of a marker indicative for CRH overactivity.

In one embodiment, the marker indicative for CRH overactivity is selected from the group consisting of a biomarker, a set of biomarkers and a clinical marker.

The one or more biomarkers may be obtained by a genome-wide screening for single nucleotide polymorphisms in patients with depressive and/or anxiety symptoms.

For example, the biomarker or set of biomarkers constituting a marker for CRH activity may be selected from one or more biomarkers of the group comprising:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,

- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In particular, the biomarker or set of biomarkers constituting a marker for CRH activity may be selected from one or more biomarkers of the group comprising:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

In a specific embodiment, the set of biomarkers comprises at least 15, at least 20, at least 25 or all of the following biomarkers:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,

- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In another specific embodiment, the set of biomarkers comprises at least 15, at least 20, at least 25 or all of the following biomarkers:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,

- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

For example, the set of biomarkers consists of the following biomarkers:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,

- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In another example, the set of biomarkers consists of the following biomarkers:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

The status of a marker indicative for CRH overactivity may be determined by a method comprising determining the status of a marker as defined herein in a nucleic acid isolated from a patient's sample, wherein the presence of indicator nucleotides as defined herein is indicative for CRH overactivity.

The term "biomarker", as used herein, relates to any nucleic acid sequence of any length, or a derivative thereof, which comprises a polymorphic variant as defined in:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,

- SNP rs11025990,
- SNP rs3758562, and/or
- SNP rs10156056.

A biomarker may, for instance, be represented by a nucleic acid molecule of a length of e.g. 1 nt, 2 nt, 3 nt, 4 nt, 5 nt, 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 60 nt, 70 nt, 80 nt, 90 nt, 100 nt, 200 nt, 300 nt, 400 nt, 500 nt, 1000 nt, 2000 nt, or more or any length in between these lengths. The representing nucleic acid may be any suitable nucleic acid molecule, e.g. a DNA molecule, e.g. a genomic DNA molecule or a cDNA molecule, or a RNA molecule, or a derivative thereof. The biomarker may further be represented by translated forms of the nucleic acid, e.g. a peptide or protein as long as the polymorphic modification leads to a corresponding modification of the peptide or protein. Corresponding information may be readily available to the skilled person from databases such as the NCBI SNP repository and NCBI Genbank.

The SNPs as described herein may be present on the Watson or the Crick strand, with presence of the corresponding base. I.e. if, for example, a polymorphism is present on the Watson strand as A, it is present on the Crick strand as T, if the polymorphism is present on the Watson strand as T, it is present on the Crick strand as A, if the polymorphism is present on the Watson strand as G, it is present on the Crick strand as C, and if the polymorphism is present on the Watson strand as C, it is present on the Crick strand as G, and vice versa. Also the insertion or deletion of bases may be detected on the Watson and/or the Crick strand, with correspondence as defined above. For analytic purposes the strand identity may be defined, or fixed, or may be choose at will, e.g. in dependence on factors such the availability of binding elements, GC- content etc. Furthermore, for the sake of accuracy, the SNP may be defined on both strands (Crick and Watson) at the same time, and accordingly be analyzed.

A "polymorphic site" or “polymorphic variant” as used herein relates to the position of a polymorphism or SNP as described herein within the genome or portion of a

genome of a subject, or within a genetic element derived from the genome or portion of a genome of a subject.

The term "wildtype sequence" as used herein refers to the sequence of an allele, which does not show the CRH overactivity phenotype according to the present invention. The term may further refer to the sequence of the non phenotype-associated allele with the highest prevalence within a population, e.g. within a Caucasian population.

The term "indicator sequence" as used herein refers to the sequence of an allele, which shows an association with a CRH overactivity phenotype according to the present invention. The term "indicator nucleotide" as used herein refers to the identity of the nucleotide at the position of a SNP or polymorphic site as defined herein, associated with a CRH overactivity phenotype according to the present invention. The term may refer to a non-wildtype nucleotide at positions of SEQ ID NO: 1 to 30 as described below:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9542951 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

The term "determining the status of a biomarker" or determining the status of a marker" as used herein refers to any suitable method or technique of detecting the identity of an SNP, e.g. at the positions of the biomarkers described herein. The determination method may be a sequencing technique or a technique based on complementary nucleic acid binding. The context of the indicated positions, as well as the strand may differ, e.g. from patient to patient, or from sample to sample etc.

The term "allele" or "allelic sequence" as used herein refers to a particular form of a gene or a particular nucleotide, e.g. a DNA sequence at a specific chromosomal location or locus. In certain embodiments of the present invention a SNP as defined herein may be found at or on one of two alleles in the human genome of a single subject. In further, specific embodiments, a SNP as defined herein may also be found

at or on both alleles in the human genome of a single subject. The presence of an indicator nucleotide or an indicator triplet as defined herein on both alleles may have a higher predictive value than the presence of an indicator nucleotide or an indicator triplet on one allele only, the other allele comprising a wildtype genotype. The presence or absence of indicator nucleotides or indicator triplets on one or two alleles may be connected or linked with an algorithm for predicting the a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms as described herein.

A person skilled in the art would be able to derive the exact position, nucleotide sequence, and indicator sequence from the above identified rs-nomenclature, e.g. from suitable database entries and associated information systems, e.g. the Single Nucleotide Polymorphism database (dbSNP) which is incorporated herein by reference. The information may also be retrievable in case of changes to the nomenclature, or to the surrounding sequence elements, e.g. based on history functions of a suitable database.

The term "isolated nucleic acid molecule" a used herein refers to a nucleic acid entity, e.g. DNA, RNA etc, wherein the entity is substantially free of other biological molecules, such as, proteins, lipids, carbohydrates, other nucleic acids or other material, such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to the complete absence of such material, or to the absence of water, buffers, or salts, unless they are present in amounts which substantially interfere with the methods of the present invention.

In another embodiment, the biomarker constituting a marker for CRH overactivity is REM density.

Such a marker or set of markers or combination of markers as described above may be used for predicting a treatment response to CRH antagonists in patients with depressive and/anxiety symptoms.

Exemplary embodiments for determining the status of a marker indicative for CRH overactivity are described below.

In particular, it has been found that a treatment response to CRH antagonists in patients with depressive symptoms and/or anxiety symptoms can be reliably predicted by using a machine-learning based prediction algorithm derived from the association of SNPs with values indicative for CRH overactivity.

The term "treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms" in the sense of the invention refers to a response in a patient with depressive symptoms and/or anxiety symptoms during and/or after the treatment with one or more CRHR1 antagonists compared to before the treatment. The response may range from a partial alleviation of the symptoms to a complete remission of the symptoms, indicated by the change of symptoms strength and/or frequency of relapse of individual symptoms and/or the mean change on a depression scale, e.g. as described herein. The response can occur shortly after treatment or after a certain time period. A decrease in symptom severity from pre-treatment of 25% or more is usually considered a partial alleviation of symptoms. Remission may be defined as achieving a value of 8 or less on the Hamilton Depression Rating Scale (HAM-D) or equivalent values on other rating scales named below.

A further aspect concerns the provision of an algorithm for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms. The method may comprise the following steps:

(a) performing a single nucleotide polymorphism (SNP) genotyping analysis in a group of patients with depressive symptoms and/or anxiety symptoms;

(b) determining a value indicative for CRH activity in each patient of the group, wherein a value indicative for CRH overactivity is indicative or predictive for a patient responding to a treatment with a CRH1 antagonist;

(c) identifying at least one SNP associated with a value indicative for CRH overactivity as determined in step (b);

(d) determining the algorithm by machine-learning from the association of the at least one SNP identified in step (c) with the value indicative for CRH overactivity.

In a step (a), a single nucleotide polymorphism (SNP) genotyping analysis in a group of patients with depressive symptoms and/or anxiety symptoms is performed.

A "group of patients" as used herein comprises at least two patients, such as at least 10 patients, or at least 100 patients, or at least 150 patients. Patients included in the analysis of step (a) may exhibit at least a moderate to severe depressive mode. The group of patients may comprise patients with CRH overactivity and/or patients with normal CRH activity.

The term "polymorphism" as used herein refers to a variation in the genome of individuals, including, insertions, deletions, point mutations and translocations.

The term "single nucleotide polymorphism" is well understood by the skilled person and refers to a point mutation at a certain position in the nucleotide sequence. In other words, only one nucleotide differs in a certain region.

The nucleotide, that is present in the majority of the population, is also referred to as wild-type allele or major allele. As used herein, this state is defined as "absence of a SNP".

The specific nucleotide that is present in the minority of the population is also referred as the point mutation, mutated nucleotide or minor allele. As used herein this state is defined as "presence of a SNP".

In theory, the wild-type allele could be mutated to three different nucleotides. However, the event of a mutation to a first nucleotide in the reproductive cells of an individual that gets established in a population occurs very rarely. The event that the same position is mutated to a second nucleotide and established in the population virtually never occurs and can be therefore neglected. Therefore, as used herein, a

certain nucleotide position in the genome of an individual can have two states, the wild-type state (absence of a SNP) and the mutated state (presence of a SNP).

The term "single nucleotide polymorphism (SNP) genotyping analysis" as used herein refers to a test of determining in one or several patients the presence or absence of at least one SNP, typically several SNPs, and in some embodiments all (known) SNPs the human genome, including endogenous and exogenous regions. In particular, a SNP genotyping analysis as used herein may not be limited to the CRHR1 gene or to genes of the CRH pathway. In other words, an SNP genotyping analysis as used herein can be a genome-wide screening for SNPs.

SNP genotyping analysis can be performed by methods known in the art such as microarray analysis or sequencing analysis or PCR related methods or mass spectrometry or 5'-nuclease assays or allele specific hybridization or high-throughput variants of these techniques or combinations thereof. These and other methods are known in the art. See for example Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Graham & Hill, DNA Sequencing Protocols (Methods in Molecular Biology) 2001; Schuster, Nat. Methods, 2008 and Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008. Genomewide arrays can be purchased from different suppliers such as Illumia and Affymetix.

For example, the determination of the nucleotide sequence and/or molecular structure may be carried out through allele-specific oligonucleotide (ASO)-dot blot analysis, primer extension assays, iPLEX SNP genotyping, Dynamic allele-specific hybridization (DASH) genotyping, the use of molecular beacons, tetra primer ARMS PCR, a flap endonuclease invader assay, an oligonucleotide ligase assay, PCR-single strand conformation polymorphism (SSCP) analysis, quantitative real-time PCR assay, SNP microarray based analysis, restriction enzyme fragment length polymorphism (RFLP) analysis, targeted resequencing analysis and/or whole genome sequencing analysis.

In some embodiments, any of the methods described herein comprises the determination of the haplotype for two copies of the chromosome comprising the SNPs identified herein.

A "subject's sample" as used herein may be any sample derived from any suitable part or portion of a subject's body. In some embodiments, blood or saliva samples are used. The sample used in the context of the present invention should be collected in a clinically acceptable manner, in particular in a way that nucleic acids and/or proteins are preserved.

The term "primer" may denote an oligonucleotide that acts as an initiation point of nucleotide synthesis under conditions in which synthesis of a primer extension product complementary to a nucleic acid strand is induced.

The term "probe" may denote an oligonucleotide that selectively hybridizes to a target nucleic acid under suitable conditions.

The primers and probes may be generated such that they are able to discriminate between wild-type allele or mutated allele of the position of a SNP to be analyzed. Methods for the design of sequence specific primers and probes are known in the art (see e.g. William B. Coleman, Gregory J. Tsongalis, Molecular Diagnostics: For the Clinical Laboratorian, 2007; Weiner *et al*. Genetic Variation: A Laboratory Manual, 2010).

Typically, a SNP is considered in the genotyping analysis if it occurs in a certain percentage in the population, for example in at least 5 % or at least 10% of the population. In other words, the minor allele frequency (MAF) is larger than 0.05 or 0.10 (MAF > 0.05 or MAF > 0.10).

For the SNP genotyping analysis a nucleic acid or DNA sample from a subject or patient may be used. The nucleic acid or DNA sample can be a blood sample, a hair sample, a skin sample or a salvia sample of the patient. Any other sample obtainable

from the patient and containing patient nucleic acid or DNA can also be used. The sample can be collected from the patient by any method known in the art. For example, a blood sample can be taken from a patient by use of a sterile needle. The collection of salvia out of the mouth and throat of the patient can be performed by use of a sterile cotton bud or by flushing said area and collecting the flushing solution.

Usually, the nucleic acid or DNA is extracted or isolated or purified from the sample prior to SNP genotyping analysis. Any method known in the art may be used for DNA extraction or purification. Suitable methods comprise *inter alia* steps such as centrifugation steps, precipitation steps, chromatography steps, dialyzing steps, heating steps, cooling steps and/or denaturation steps. For some embodiments, a certain nucleic acid or DNA content in the sample may be reached. Nucleic acid or DNA content can be measured for example via UV spectrometry as described in the literature. However, in alternative embodiments SNP genotyping analysis may also be performed by using a non-extracted or non-purified sample.

DNA amplification may also be useful prior to the SNP analysis step. Any method known in the art can be used for DNA amplification. The sample can thus be provided in a concentration and solution appropriate for the SNP analysis.

The analyzed SNPs may be represented by values 0, 1 or 2. The value "0" may indicate that the SNP is present on none of the two homologous chromosomes. The value "1" may indicate that the SNP is present on one of the two homologous chromosomes. The value "2" may indicate that the SNP is present on both homologous chromosomes. Homologous chromosomes correspond to each other in terms of chromosome length, gene loci and staining pattern. One is inherited from the mother, the other is inherited from the father.

In a step (b) of the method for providing a prediction algorithm, a value indicative for CRH activity in each patient is determined.

Steps (c) and (d) of the method for providing a prediction algorithm may analyze the association of the analyzed SNPs with the value indicative for CRH overactivity and/or normal CRH activity and generate an algorithm for predicting the treatment response to CRHR1 antagonists.

In an exemplary embodiment, the group of patients may be split into two sets of similar size and similar values for descriptors such as demographic descriptors or clinical descriptors. These two sets are hereinafter also referred to as "training set" and "test set".

In step (c) of the method of this exemplary embodiment, at least one SNP associated with the value indicative for CRH overactivity as determined in step (b) is identified in the training set.

Further, there can be at least two alternatives for the result provided by the prediction algorithm. First, the result may be a categorical answer whether the patient responds to CRHR1 antagonist treatment or not. Second, the prediction algorithm may provide the answer to which degree the patient responds or does not respond to the treatment. Depending on the desired result provided by the prediction algorithm the way of determining the algorithm may differ.

In the alternative that the prediction algorithm will analyze whether a patient responds or does not respond to CRHR1 antagonist treatment, the values indicative for CRH activity may be provided as logic data variable (Boolean type; 0 vs. 1; true vs. false, high vs. low responder). Therefore, if the test performed to determine values indicative for CRH overactivity provides a data range, the patients may be dichotomized by a threshold into high vs. low responders.

In the alternative that the test will analyze to which degree the patient responds or does not respond to the CRHR1 antagonist treatment, the values indicative for CRH activity may be provided as numerical values.

Typically, SNPs that are modified in a significant percentage of the population are used in the method for providing a prediction algorithm. For example, only SNPs with a minor allele frequency (MAF) greater than 0.05 or 0.10 may be selected for further analysis. This means that only SNPs that are modified in at least 5 % or 10% of the population are selected for further analysis.

Association for all SNPs with the value indicative for CRH activity is tested by an association analysis testing the likelihood for a patient to be CRH overactive vs. CRH non-overactive in dependence of the genotype of said patient. Said association analysis may be conducted for example by an additive genetic model and/or by a logistic regression. A SNP is e.g. identified to be associated with a value indicative for CRH overactivity if the corresponding p-value is at least $1 \times 10^{-3}$ or at least $1 \times 10^{-4}$ or at least $1 \times 10^{-5}$. The lower the p-value the more the SNP is associated with a value indicative for CRH overactivity. Accordingly, a SNP is e.g. identified to be associated with a value indicative for normal CRH activity if the corresponding p-value is at least $1 \times 10^{-3}$ or at least $1 \times 10^{-4}$ or at least $1 \times 10^{-5}$.

In the step (d) of this exemplary embodiment, the algorithm for predicting a treatment response to CRHR1 antagonists may be determined by the use of SNPs in the test set by a machine learning method.

The term "algorithm for predicting" as used herein may refer to a classification function (also known as binary classification test).

The term "machine-learning" as used herein may refer to a method known to the person skilled in the art of machine learning. In particular, machine learning is concerned with the design and development of algorithms that allow computers to evolve behaviors based on empirical data, such as from sensor data or databases. It may be selected from the group consisting of artificial neural network learning, decision tree learning, support vector machine learning, Bayesian network learning, clustering, and regression analysis.

The term "reliable prediction of the treatment response to CRHR1 antagonists" as used herein may refer to a high performance of the prediction algorithm. The evaluation of the performance of the prediction algorithm may depend on the problem the algorithm is applied for. If the algorithm is used to identify patients that are likely to response to the treatment with CRHR1 antagonists the performance is usually expressed by a high accuracy and/or sensitivity and/or precision. If patients should be identified which are likely not to respond to the treatment with CRHR1 antagonists, specificity and/or negative predictive value are typical statistical measures to describe the performance of the prediction algorithm.

For optimizing the prediction performance of the algorithm, the step of determining the algorithm by a machine-learning method in a first subset of the test set and testing the prediction performance in an second independent subset of the test set may be repeated based on different numbers and groups of SNPs, until the desired prediction performance is reached.

Accuracy, sensitivity, precision, specificity and negative predictive value are exemplary statistical measure of the performance of the prediction algorithm. In the following, examples are given for determining the performance of the prediction algorithm.

As used herein, accuracy may be calculated as (number of true positives + number of true negatives) / (number of true positives + number of false positives + number of true negatives + number of false negatives), e.g. (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The accuracy of prediction may e.g. be at least 60%, at least 70%, at least 80% or at least 90%.

A used herein, sensitivity may be calculated as (true positives) / (true positives + false negatives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The sensitivity of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, precision (also referred to as positive predictive value) may be calculated as (true positives) / (true positives + false positives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). The precision of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, specificity is calculated as (true negatives) / (true negatives + false positives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). The specificity of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, negative predictive value is calculated as (true negatives) / (true negatives + false negatives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The negative predictive value may be at least 60%, at least 70%, at least 80% or at least 90%.

Other statistical measures useful for describing the performance of the prediction algorithm are geometric mean of sensitivity and specificity, geometric mean of positive predictive value and negative predictive value, F-measure and area under ROC curve, and the positive and negative likelihood ratios, the false discovery rate

and Matthews correlation coefficient. These measures and method for their determination are well known in the art.

In general, a prediction algorithm with high sensitivity may have low specificity and vice versa. The decision to select an algorithm having certain statistical characteristics such as accuracy, sensitivity or specificity may also depend on the costs associated with a treatment with a CRHR1 antagonist should the prediction be positive and/or whether such a treatment is detrimental in cases where the result is a false positive.

For a prediction whether a patient likely responds to the treatment with CRHR1 antagonists the prediction algorithm may be based on a number of SNPs sufficient to achieve a prediction sensitivity and/or precision of at least 55%, optionally at least 80%.

For the prediction whether it is unlikely that a patient responds to the treatment with CRHR1 antagonists the prediction algorithm may be based on a number of SNPs sufficient to achieve a prediction specificity and/or negative predictive value of at least 55%, optionally at least 80%.

For a prediction whether a patient responds to a treatment with CRHR1 antagonists or not the prediction algorithm may be based on a number of SNPs sufficient to achieve sensitivity and/or precision and/or specificity and/or negative predictive value of at least 55%, optionally at least 80%.

In one embodiment, a number N of SNPs is associated with a value indicative for CRH overactivity or normal CRH activity in step (d) of the method for providing an algorithm and/or the presence or absence of a number N of SNPs is determined in step (a) of the method for predicting a treatment response, wherein N is sufficient to provide an accuracy of at least 80% and a sensitivity of at least 70% and a specificity of at least 70%. In another embodiment, a number N of SNPs is associated with a value indicative for CRH overactivity in step (d) of the method for providing an

algorithm and/or the presence or absence of a number N of SNPs is determined in step (a) of the method for predicting a treatment response, wherein N is sufficient to provide an accuracy of at least 85% and a sensitivity of at least 80% and a specificity of at least 80%.

Typically, at least 10, at least 20, at least 25 or at least 30 SNPs are used for determination of the algorithm in step (d) of the method for providing a prediction algorithm.

The skilled person in the art knows that the use of different machine-learning methods and adapting parameters used therein can be also used for improvement of the prediction reliability. The whole statistical work-flow can be automated by a computer.

Another aspect is a method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, wherein the method may comprise the following steps:

(a) determining in a nucleic acid sample obtained from a patient the presence or absence of at least one single nucleotide polymorphism (SNP) associated with a value indicative for CRH overactivity;

(b) predicting the treatment response to CRHR1 antagonists by linking the prediction algorithm provided by the method described above with the presence or absence of the at least one SNP determined in step (a).

"Linking an algorithm for predicting a treatment response to CRHR1 antagonists in patients having depressive symptoms and/or anxiety symptoms with the presence or absence of the at least one SNP" as used herein may refer to using such an algorithm to predict the treatment response based on the determined presence or absence of the at least one SNP, e.g. by integrating the at least one SNP determined in step (a) of the above method by the algorithm.

In one embodiment the method comprises a further step of obtaining a nucleic acid

sample from a patient preceding the step of SNP determination.

In one embodiment of the method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, step (a) comprises determining at least one of the SNPs, optionally all of the SNPs which were associated with a value indicative for CRH overactivity when determining the algorithm by machine-learning from this association.

Typically, a SNP is considered in the genotyping analysis of step (a) of the method of prediction if it occurs in a certain percentage in the population, for example in at least 5 % or at least 10% of the population. In other words, the minor allele frequency (MAF) is larger than 0.05 (MAF > 0.05) or 0.10 (MAF > 0.10).

For the SNP genotyping analysis of step (a) of the method of prediction, a nucleic acid or a DNA sample from a patient may be used. The nucleic acid or DNA sample can be a blood sample, a hair sample, a skin sample or a salvia sample of the patient. Any other sample of the patient containing nucleic acid or DNA can also be used. The sample can be collected from the patient by any method known in the art. For example, a blood sample can be taken from a patient by use of a sterile needle. The collection of salvia out of the mouth and throat of the patient can be performed by use of a sterile cotton bud or by flushing said area and collecting the flushing solution.

Usually, the nucleic acid or DNA is extracted or purified from the sample prior to SNP genotyping analysis. Any method known in the art may be used for DNA extraction or purification. Suitable methods comprise *inter alia* steps such as centrifugation steps, precipitation steps, chromatography steps, dialyzing steps, heating steps, cooling steps and/or denaturation steps. For some embodiments, a certain DNA content in the sample may be reached. Nucleic acid or DNA content can be measured for example via UV spectrometry as known in art. However, the SNP genotyping analysis may also be performed by using a non-extracted or non-purified sample.

Nucleic acid or DNA amplification may also be useful prior to the SNP analysis step. Any method known in the art can be used for DNA amplification. The sampled can thus be provided in a concentration and solution appropriate for the SNP analysis.

The analyzed SNPs may be represented by values 0, 1 or 2. The value "0" may indicate that the SNP is present on none of the two homologous chromosomes. The value "1" may indicate that the SNP is present on one of the two homologous chromosomes. The value "2" may indicate that the SNP is present on both homologous chromosomes. Homologous chromosomes correspond to each other in terms of chromosome length, gene loci and staining pattern. One is inherited from the mother, the other is inherited from the father.

In order to determine SNPs, SNP-specific primers and/or probes, a primer extension reaction, SNP microarrays, DNA-sequencing may be used. These reagents and methods are routinely used in the art (see for example Chen, PCR Cloning Protocols (Methods in Molecular Biology) 2002; Schuster, Nat. Methods, 2008, Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008). For example, MALDI-TOF (matrix-assisted laser desorption ionization time of flight) mass spectrometry on the Sequenom platform (San Diego, USA) may be used to genotype the selected variants. For primer selection, multiplexing and assay design, and the mass-extension for producing primer extension products the MassARRAY Assay Designer software may be used using the sequences presented in table 2 as input. The MassARRAY Typer 3.4 software may be used for genotype calling. Any other reagent or method known to the person skilled in the art may be used in order to detect the SNPs in an individual.

In one embodiment, at least one SNP determined in step (a) and used for the prediction algorithm of step (b) is a SNP selected from the group consisting of SNPs as shown in table 2 and an SNP in strong linkage disequilibrium with any of the SNPs shown in table 2.

**Table 2:** SNPs (together with flanking sequences) which may be used to predict the response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms. The position of the SNP is indicated in bold as **[wild-type allele/mutated allele]**.

| SNP_ID | SEQUENCE |
|---|---|
| RS6437726 SEQ ID NO. 1 | CAAGAAAGAGAGTAATAAAAATAACCACAATGAGGGCTCTCATTAATACT GGATCTTATGGAAACCAATTGTTCAGTCCCTCAACAAAAGACCAGATGG GCAGGAAGCTAAATATACACCATGCACTAAACATTATGAGTATCATAGTT TACAAGTCAAAGGGGGCTCTATTGAAGATAGTTCTATTTTCCCTCTATAT T**[A/G]**TCTGCTAGACAATACCTGATAACATTATCCAAGTAAATGACAACTT GATAAATAGTAATTTCCAATGGTGAACAGAGGTGACATTTCCTCATTACA AAAATATTTTCTTTGGCAGATGAGATTAACTGAATAAGAAATCCACTGAC ACTGAAATCACAGAGCCAAATTCCCTATCACAGCACTTATCACATTGCGT TAGG |
| RS1986684 SEQ ID NO. 2 | TTCCTTGTAGCGGGGAGAGAGACTCAGGGAAGGCAGGGTGATACCTGA GTTGGGGCTTAAAGCAAGGTAGGGTGTGTGTGGTGATGGCAAAATAGG TAGGAAGACAGCACGGGCAAAGTCCTGGAGGCAAGGACAGAAAGAGGA AGTGGCAGGAAGTGAGGCTGGGGAAATGAGTAGGGGTCAATCATGATG TTTCTGGT**[A/G]**TAGGGAAGAGTTTGGAATGCATCCTCTAGGCCATACGC CATTGGGGGCTTTTAAGAAAGACAGTGATGTTGGTTTGATTTGCATTTTA TATAGACTTTTCTGGCAGCTGAGAGGAAGGTGGTTTTGAGAATCACAAA GCTGCGGGAAGATCAGTCAGGAGGGTTCTAGAATAATCCAGGCAAGAG CTGATGGGGACTGAG |
| RS7380830 SEQ ID NO. 3 | ACAGGGGTGGCTACTCTTTCTCCAGAAATAGGTGTCCTGTGGGGCATTT TGAAGTAGAATGTTGATAGTTGCTTTCAATTTTAGACTGGTAAATAAGAAT TGGGCATTTGAATTTCAATATACTCACTGTGTAACTGTTATTGAGTATGCT TTAAGTGACCTATAATACTGCTTCATTTAACTTTATTGTCCTAATAACT**[C/T]**TCTTAGAGTGACAATAACTTAGGTTAGCCACTTGCCTAGGGTTCTGAA ACCAAGTAAATGGTGGAGCTGGAATTGCTGTTCTTGTCAGTCATTAGACT AGATCGGTTTTCTTCTTCCTACAAATTTTATATACTAAAAAATTTTGAAAAA AGACATTTTTCTTTGGGAAAAATAGGGAATGTCAGATCCCTTTGGAGATG |
| RS3903768 SEQ ID NO. 4 | CTCGCAGCAACCAAGCCTGCCCAAGCCGGGGAAACCTGGGGAGCAAAC CTTCACCTGCACTGTACATCAGAGACCAGTTGGCCCTATTTTGGCTCCT GTGGACAGGTAAGTATCCCTTTTGACTCATCCCCCAAATATCAGGTGAG CCAGGAAAATAAGGCCTTTGGCTTAGACAGTCAATTCAAAGTCTGCCAT AGCAT**[A/C]**CCTAATTACATCCCTATTGCCCCTTTTCTAGGTCGTTTCTCC TCTAACACGATTTTATTTTTCTGTCAGCCATTTTATTTTATTTCTCACCTTG AAATATATGTTTTCTTTGCAGTTTTTGCTTTGGCTTCCTGCTAACTCTATT TGGGCAATTGTTTAAGGCTGAACACTTGGTTATGAGAGGTACCCTGTTG TGTTGA |
| RS7325978 SEQ ID NO. 5 | TCATCAAGTCTCCTTTTTCTCTAGGAAAAATAACATTGTCAAGGTTATTAA CAGTCAATAAGCTGTCATAGGCTCAGCATGGATGGGGATATTGGGTTTC CTTGTGCTTATATGAAAGATGGGAAAATCCGAAGTTCTTTTCACCCTGAT ATGGAAAATACCCAACATGAGGAGAAGCAGCAGCTATATGATTCTGAGC A**[C/T]**AGAATGGGAGTAAGAATAGGGTCATGCTGTACTGATTATCTGCTA ATAAAATGCAAAAGTGTTAGGTAATTTCATCAATATCCAGTTAATACTAAT ATAGTTAATATTTCATGACTGGGTAATATTTTATAATGATAAATATTTTTAT AGATCTTAGCTCTTTTTATTCTCATATCAACTGTATGAAATCAGTGATTGG T |

| SNP_ID | SEQUENCE |
|---|---|
| RS13585 SEQ ID NO. 6 | CTGGGGACCTCAGGGAGAGGTACGCAGGTTGCCATGGCTGCGTCTGCA GTCCACCTGCCTTTCCACGCCAGGGAGTCAGTGATGTGGAGCCCCCTG GGCCCCAGTGGAAGCAGCGATCAGACTATGTGTCCTTGAAATAATGTTT ATTCCACGCTGTCCCGACAGCCCCCTCTGCAGGTCCCCT**[C/T]**GGTGTA CTCTGAGGTGGGAAACCCTCCCTGGGGGCGGTGAAGGGGAACTCGGG CCACCCCACCAGCCAGCAGATGCTCCAGCAGCCAGAGCCCCAGCCTGG AGCTGAGGCTCTTCCTGGGGCTCGCCGGGCCCCTGCAGGCTTTTCGGA CCCTCAGCCAGCCCGGCTTCCTCTGCTTTGGGCAGCAGCAAGCTGGCC CTT |
| RS9368373 SEQ ID NO. 7 | TTCCTGTGCCTCAGCTCCTCTGTAGAATGGTGCTGGCAATACAGTTTGC CTCATTGGGCTCTTGTAAGCTTTAAATAGGTTATTATACATAAAGAGCTA ATAGTGATGCCTGTAGCCGTTGTCTAAGTGCTAGCTCTGATGATGGTGA CAAAGAAGTAATAGCAATCAGTGGTTTAGATTAAACCATTTTAGGCATAA AC**[C/T]**GTTCTGCTAGAATCCAAGGGGAGATTTTTTCCCATCAAGGAGAC ATAGCTTGTTGGGAAGATAAGACATACCCAATTGCAGAAGTAATTAATTA ATTCTTTTTTTTTTTTTTTTTTTTTTTTTTTGCGATGGAGTTTCGCTCTTGTT GCCCAGGCTGGAGTGCAATAGCATGATCTCGGCTCACCACAACCTCTG CCTCCT |
| RS10935354 SEQ ID NO. 8 | ATAGGCCCTATACAGCTCTCAATTTCTTTAATCAATCTTCCTAGCAGCCC GTGAGAAATATTACTGTCTTCAGCTTCCTAAAGGAGAAAACAGAGGCCT GGAGGGATTAAAAGACTTTTCTAAGATTTTAGAGGGCATGTTAGGGTTCA GGCCCAGGGCTGTCTAACCCAAGGCCTAATTCCTTCTATTACATCCATC AT**[A/G]**CATGAGTGAGCACTGGGCATGAGGATACGTCAGTGAAAGGGGC CCTGTAACATGGACCTTACATTTTGGCTGGGGGAGACAGGCAATGAATA CATAGGACCATGTTGGGAAGTGCTAAGTACTCTGATGATAACACAGCAG GGTGAGGTGACAGAGGTCTAGGGAGAGTGGTGTTCAGCAAAAACTTCT CTGGGGAGAGA |
| RS8095703 SEQ ID NO. 9 | AAAATTTACCAGGTTTAAAAAAAAAAAAACTCAAATGATATTTCAGAAACC TACCCCTTTCAAAACAAGGAGGAGAAAAATCTTCTCCACAAAAGCACATA TTGAAAAAATATTTTGGGGGCAAGGCCTGAAAGGGTTGGCAGTGTGCAG TTCTGTTATTATTCCCGTGGCCATTTTATGGGCCTCAGCAAAACACTGGG **[A/G]**TCATTATCTGTCTTCTGGTTACTCCAGGAGAGCTAGCCATCACAAC CCAATGGAAGAGACTTCAGAGAAACCCACACAGGCACCAGAAGTCCTTC CCTTTCATCTGCCACTGTGGGGTTTTGTCCTCATCTATTACAATGTTGTC CAATCTCAGACTGCATTCAGAACAAAGGCTCTCAGACTGAGGATGAGTT CTTGGA |
| RS10206851 SEQ ID NO. 10 | CCAAATAATTGTTATTGTTGTTTTAACATGGCAATCACGTTATTTGCCATA TGTGAAAAAGAATATTTAAAATGCTTTTTAAAACTATGTATGTAAAAGAAT GTTTAAATTGTTTTAAAAATATGTTATATCTACCTTGGCACCATCCTTGCT GTTGAGAAATGACTTTTACCTGCTTACTTAGAAGGAAATGTCAGAAG**[C/T ]**AGAAGTACATTTGAATACGATTATTTGAAAGCTTCATCCATTTTTCAAAG AATGTATACAGTAACACTAAATAGAAAGCATAGTTTATCAACTCTTCACTA AGAACAGTCTAGCAAGTATATCAGAGTGGCTGTGGTTCCAGTTGGACTA ACCTAATCATTTATGAAAAGGTGATAATAAGCTTGGACCAAGAGCACCCA |
| RS9542977 SEQ ID NO. 11 | CAGATGTTATGTGAAACTCTGGAGAAATAGTAGCAAGCAAGACTCACAT GCCTCCTGCCCTCACAGAGCTCCATGATCTGGTGAAAGTGCCAGATATT TAAACCCATGGATGTGTGCACACAAAATAACAATTCTCTCAAGCGTTGTG AAGAAAAGTCACAGAGCACTACAAAAGCATGTAAGAGTGAGGCAAAACC TAT**[C/T]**GTGTTAGGACAGGGAAGGCTTCTGTGAGCTAACCTGAAGGAT GAGTAGGGGTGAGCCAGATGAAAAGGCGAGAGAAAAACATTCTGAGCA GAGACTGCCACTGAGTGCATCCCAGTTTTCCCAACATCTTAACACTGTAT AATGACTACACTGGATTTTCTTCATCCTGGATCCATGGTTAGACATGTTA ATATGCCTTC |

| SNP_ID | SEQUENCE |
|---|---|
| RS4942879 SEQ ID NO. 12 | CCCAGTCTGTGGTATTTTTTTATAGCAGCACAAACAGACTAACACAAGAG GTGGATAGGATTTGCGAGCATGGACCTTGGAGGTTTGTGGCCTCAATTT AAAGTGAGTACATTCACCCAGCTGGTGTTTTTCTCTTGCTGCTTGGGCA CAGAGATGGAGTAAATGGGTCTAATCAAGGATAAAGGGAGAGCCAAAGA GAT**[A/G]**GTAATATTTGAAAGGAAGTGTTTTTAATGATGTGCCATGTAATC TGAGCTGGGTCAGGAATGAAGTGAAAAACTAAGAGATGATGGATGATGA TAGGGGCTGTGAAAGGAAAACAAATCTTGGGGCCCCCAAATCACTAAGC TAAAGGAGAAAGTCAAGCTGGGAACTGTTTAGGGCAATCCTGCCTCCCA TTTTATTCA |
| RS9542954 SEQ ID NO. 13 | TATTACTGCTGAGAAAACTGGGTTTGATAAACTAAAGATGCCCATGTATA TCAGTCATGCTCCTGGTGAGAACAGGTGGCTCACTGCATAATGAGAGGA ATATTCAATTAACTATTTACAAAGCTATGGATGACATGTAGGGAAGCCAC AGAGAGAGTACAGTATCTAGAGCTAGTAAGAGTAGAAGGCCATCACTGT CC**[A/C]**CAGGCCTAAAGGAGGTAGAGCAGTCAAAGGAAACAAGAGACAA GGGAGGCTGCGAGGACAGGGCCACCTGGCAGAGCCATAACCTTAAACT AGGTAGTCACTTCTTGGCAACTCTGCAGGTAGGGAGCCAACCTCACTTT TAACCCTCCCTCTGATGCCCAGCTGGTTTACCCCATTGGTGAAAATCAG TGGGTGAGGGA |
| RS1593478 SEQ ID NO. 14 | CATGAAAAGATACTTAACATTGTAACATCTTTGCATTAGGGAACTGCAAA TCAAAATCATAACAAAATAGTACTGCATGCTCATTAGGATGACTATAATC CAAAAGAATAAAAAAGAAAATAACAGGTGTTGGTAGGGATACAGATATAG AGAAACTGGAGCTCTCATGCCTTGCTGGGGGGCATGTAAAATGATTCTG C**[C/T]**GCTTTGGAAAACAGTTTGGTGGTTCCTCAAAAAGTTAAACATATAA TCCAACAATTCCACCCAAAAGAATTGAAAGCAGGGTCTAGTACACCAAC GTTCATAGCAGCTTTATTCACATCAAGCCAAAGGTGGAAGCAGCCCAAA TGTCTACTGATGGATGAGTTGATACACAAAATGTGGTATATATATGCAAT GGAATA |
| RS9542951 SEQ ID NO. 15 | GCCACTTGAATGCCCCAAAATGGAGAGATGGGCGTGGGAAGAGAAAGA CACCTCAGCAACACAGAGCTGAGAAAACACTGTGAGTTTTATTTAATTCC TACTTACCGTTATTTTGCATAGTAAACAAAAGGGATATTTTTGAAAATCCC TTTGGATAATTTCTGCCACCTAAAATTCTGAGCATTTTGACTCACTGCCTT **[A/G]**TAAAAAGAATCAATTAATTGAATAAGAGAAGGGATTCTCCCCTGAT CTTTTCAAGAATCCTTAAAAGGCACATTTCTCACTAAGGATCTTGAAAGT GTATTTCTAGCCAATCCCAGGAGTCACTGCTCAGAGATTTACATTTCACA AATGTAATCAACAGCCTAAGCAGAATATTGACGTTTGGACTGCAGAGCT CTGCT |
| RS2188534 SEQ ID NO. 16 | AGGGTCCCCAAATATTTCCATTTGAGATGACAAAGTGCTCTTCAGTCATT TAGCTTACTCTTCAGTTCAGATGACTTATCATCTTGATTTCAGAGAGTTCA TATATGTCTGTTTTAAAAAACTGGTTCAAAAAGTCTGAAGTTACGAAACTA AACCAAATATGCATTACTCTCATGTCAAATTACAAGCTCTTAGCTGC**[G/T]** GGGATTTTTTCACATGCAGCCTGGAGCCCTTGAAAACCTCTGTTTTCTGT TAGACTCTCCAGGGTACACAGAAGTTGCCTCATTATTTTAGTTAATGGTG ACTGCAAATAAGCCCCCCAAGTCATTTAACTATGTGCTTACCACTGCTTT AAAAGAACCCCAAGTTAGGTCCTCATGTAGGTAAAGGAGCTCCCTTCAC A |
| RS12524124 SEQ ID NO. 17 | ACTTGGGCCCAAAGGCATTCAACTAGAAAGCTGGTAATAATAACAGCGA CAGTTTATTGAGTCTTAGTGTTTCTGAGAACTTTTCTAAGTACTTTACACA TATTAAATTTTTAAATCTTCACATTAGTCCTGTGAGGAAGGTACTATTGTT ATGTCTGTATTACCCATGGGGATACTGACGCACAAAGAAGTCAAGTAAT**[ A/G]**TATTTAAGATTCTAGTAAGTGCAGAGCCCAGGTGCATGCAGTGCCT GGGCTCTGCCACCCATGCAGTGCTGACTAGGGCTTCCACCCATGGATTT TTTTTTTTTTTTTTTTTTTTTGAGACAGAGTTTCGCTCTTGTTGCCCAGGC TGGAGTGCAATGGCATGATCTCGGCTCACCACAACCTCCGCCTCTCGG GTTCAA |

| SNP_ID | SEQUENCE |
|---|---|
| RS4352629 SEQ ID NO. 18 | CCCATAATAATGAAGGATTGGACCTGATAATCTATCAGGTACATTTTAGC CTGAAATTTATTTGTACACACGCACAAACACAGACATGTGCACACACACA TACACATATATATATAACATTTATAAATTTTAAAACATAAAGCTATACTAGA AATGAAAGCTTATATATTGAACTGCCCCACCTTTCTATTTGCAGCCAG**[C/T]**TACCACCCCAGTCTAATGTTTCACTTTATATAAATTCATTTATTCTTTTA CTCATTTCAAATATATGATGATGTAACTATAAAATCAACATTTAGTCACTC TGAATAACCCAAAATAGCAAATAATTTAAAAATCACTTCCACTTGACTTTA GAATCTATTACATGCATTGTTTTTCCAGAAAATTTACCTCATAATTAT |
| RS7448716 SEQ ID NO. 19 | CTACTTATATGATTAGAGAACAAGAATACTAGGGGGAAAATCAGCATGCA TATAATCTAAGAAATTGTCATTATAATTTTAAAATCCTTTGCAAAATCAGTA AATATGAGTTTAACTTATATAATGATACACACACACACTGATATGATGCTT TATTGTCTAAACACTGGCTGCTTGTGGAGACGTATTCTGGTAACAAA**[A/G]**AATATAGCATCTTAAAATTGATGCTAGCATTGTATATCCAAATAGAGAGT AAATGCAACCAGAATATTTTTTATATGTTTAACATTGTAGTGTTGCTGACA TCATTATATATTTGGTTATGTTAATCTCAAAATGCACAATATAGCTGTATG ATCTGTATAATGCAAAAAAATGTAGAGCTTCATTTTGATATTTATTAT |
| RS11873533 SEQ ID NO. 20 | CTGGAAGGGAACAATGGAAGAGGTGCATTAGTCACATTCCAAAATGCAG GAAGCAATAACATGTGGCACTATTGTCATTTATGTAGCACCCTAAATACT GGGACAAATGACATAGATGCCCTTCTGTGATTACTAAACTCCCCCACAG TGTCTCAGAAGGAAGAGCTTTTGACAGGAAATCATCAAGATCTGATGAC ATT**[A/C]**GAGAGCAATTAACATTCTCTTCAACCATGAACTAATTGCCTCAT TCACATTTTTCTAGCCATCCTAGGAAGCAGATAATAAGCAGCAATTGTCC TGCCCAGGAATTCTGACTTGTGTAATTTGTAAAGCTTTTCTTTGTATCTAT TTCTTTCCTGTGGCCATCTTTTTGTTTTTGGACTGTTTGGTAACAGTAAGT GGGT |
| RS10062658 SEQ ID NO. 21 | ATCATTCAGTATTAAGAGAGAAATGAATACATTTTCAGATATACAAGAATT CAGTTTACCTCCCACAGAATCTCTGAAAAAAATATTAGATTACTATAGTTA AAAAGGAAAATAAAATAAGTCCTGTTAGAAATAATTGGTAAAAAAGCAAA GGTGATGAAAACTTATTGAAATATATTATTAAAGTAATTGTTAAAAAT**[A/G]**TACACTAAATCTAGAATATATAAATGTAGCAGTTGTTAAGGGGAAGGGGA AATAGAAGTGGAAGAAAATGAACATTAGAACAAATGTTTAGCAGTGGGAT TATTTTATTGGAAGTCTAATGTAAGAAGTATATTCTCCAGGGAGGTATTT CAAGGACATATGAATAGTAAAGGGATAATAAAACAACTCTATAAGGTAGT |
| RS12547917 SEQ ID NO. 22 | CACACACAACGCTGGGCCCAGTAAATAAGTTTTGTTTTTTCCCAGGGAA AAGTTGAACAACAATGGTGAGACCAGGAAGGCTCTCCGTTCACAGGAAA TACTGTGTCACCGCTCGGCCGCAGGCTGTGTGAGGTCACGGGCGACGC TCGGGTCACGTGTGGCGGCTCCTGTTCACAGTGCCGTGTGTGATAAACT GGGAC**[C/T]**TTCTGGTGAGGGGAGACTGGCGGGGGGTGGGGAGGGCA AGGAGTGGGAAAGTCGCCTATAAATGTTTAACAAAAGATCCGCAATGGG AACAGGAACTTGCATTCTTTCTTTCAATGGACAAAGCTTCCACATCAAGA TACGCTTGTGTGCTGGGACCAAATGCCACAGTGCGGCGAAACTCGTGA GCACAAGTCCTGCGT |
| RS1038268 SEQ ID NO. 23 | ACAACAGGGTATCCTAGCCCAGCAAAATTGACTCATAAATTTAATGATCA CGCAATTGGTAATTCTAAATCCAGTCAGAAGTCTACATTCTGTGTCCACA GTGTCATGTCTAGATGTTGGTCCAGTCTCCCATGGACTGTGCCTTGTTAT TTGTTTTCTCTTTGCTAAGCCACATCCCCTGAGGGCTCTGTTTATGCTCA**[C/T]**TGCAAAATCTTTGACTTTTTAACTTACTGGGCATATTGTCTTCCTACT TTTGTTCTCTTCTGTTATTTTATTTACTTGACTCTGACATGTCTCATTCCC |

| SNP_ID | SEQUENCE |
|---|---|
| RS2375811 SEQ ID NO. 24 | TTTCAATGGGACTGGTTGGACAGTGGGTGCAGCCCATGAAGGGCAAGC CAAAGCAGGCCGGGGCATCACCTCACCCGGGAAGCACAAGGGGTCAG GCGATTTCTCTTTCCTAGTCAAGGGAAGCCATGGCAGACTGCACCTGGA AAAACGAGACACTTCCACCCAAATACTGCGTTTTTCGCAAGGTCTTAGCA ACTAAC**[A/G]**GACAAGGAGATTCTCTCCCGTGCCTGGCTCGGCTGGTCC CACACCCACGGTGACTTGTTCACTGCTAGCACAGCAGTTTGAGATCGAA CTACGAGGCAACAACCTGGCTAAGGGAGGGGCATCTGCCATTGCTGAG GCTTGAGTAGGTAAACAAAGTGGCCAGGAAGCTCGAACTGGGTGGAGC CCACTGCAGCTTAGCA |
| RS1352671 SEQ ID NO. 25 | ACTTTAGGGACTTTGAGTGATGGACAACCCCCTATCAGATATCATCAGC CTGAAACATCCTTATCTTGGCATTAAATTAGAAGGAACCCCAGACCCTGC GTACCAGAATTGTTAGAATCACAGTCTCAGTAAAGAACCAACTCCTGATC ACTTCTCTAAAGGAAAGTTCTAGAAGTCTGCACACTCTGCAGTCACTTTC A**[A/C]**TTCTATCCAAGTGTACACTTAGAACTCTAGAAAACACTACGGACA GTCTTCAGCCAGGTAAAGCCTAAAACCAGCAAAGAACAGGGAGAGTGA GGGA |
| RS364331 SEQ ID NO. 26 | CGGATTATCACAGTTCTCAAAAGAGGAGTATGCATTTGCTTGCTCCAATT CCTCTTCTTCTACACTCTCTTAAGCATTCCTCAACCAGTCTAATATCTCAT AGTTCCCCAAAACTGCTCTGTTCAAGACCATTAGTAAGATCTTTGATGTT AATCTGTGGACCGTATCTCTGTCCTTATTTTACTTGAAGCCCAACAGCA**[ A/C]**ATAAAAAAGTTGTTCTCCTCTCCTCCCTGCTACACTTTCCTTATGTG GCTTGCTGGGCTCCTCAGTCCCCTGTGAAAAACTCTGACATGGAGATAC TGCAGACCAGTAGAAGGGCTGGGCAGACACTATACAGAAACAGTATGC CCTACATGCTCCTTGGCTAAATCTCTAGAATTTTTTTCAGAACTCATCCA CAAATT |
| RS1924949 SEQ ID NO. 27 | ATTTTATCTCATTTACTTATTAAATCAAACCAATATTTTATGAAGTGATTCC AGTATTGGAATAAAAATGTAATTCTTTAATCATTAAAAAATCTTTATGAATA CCTTACATCAACTGTAGGGGACCAACCAGGGAAAAGCAGGGAGACTTG TAGAATCTACACCTCCAGAACAACCGACCTCCATCTTCTGGACAACTC**[A/ G]**TCTTCTAAAGTGCAGGACAGACTAGTTGGGGGAGAAAGGAGGAAATG AAAGAGATAGACTAAAAGGGAGGGAGAGAACAGATATTTTTTAAGTACC TGTTATGTTCTGGATACAGCACAGAGTACATTGTATCTATTATTATAAGG CATAAAGAAAGATTTCTCAGGTTTTTGGAGTCAGATTGCAATATAAAATA ATAG |
| RS11025990 SEQ ID NO. 28 | TAACTTCAAATTGTTTTGCAAAATCTCTGTCATAAAAATGCTTACCAACAA ATACTGATACTAAATTTAGATGTGGGGGTATTAGTTATAATCCTGAAGTG GGAGGGGGAACTTCTTAATTCCAATTTAGTTCTAAGAGAAGGAAGAGTA TTTAGGCCCAGAGAAGGTTACGCTTAAAGGTCTGATAGTGTTTTCTTTGA **[A/G]**AAATATGTCTCAAACTAGAGAATAAAACTAATTATCTCATCTAAGTT ACCTAGAGACATTTATGCTCATCAGTTTGATAAAGGACTGCAAGTAGACA CAGAAGCTGTATTTTCAGTCTTGAACCCAGCAATAGTACATTAACAAGAT TGGGGCAAGGCAAAGGGACTTTTGTGGCACAAGATACAATATATGGATT GCGT |
| RS3758562 SEQ ID NO. 29 | CTCTTCAAAGGCCTTTGCCCTTGGGTACCACAGGTTCTGAGACAAGAGG GCTATGGAGAGCCCCCATTATAGCTGGAGCCTCCTGCCCTGCCCAAAG GTGTGACTTGAAGGGTGGAATTTCAGGCAGCGTGGCTCGCCCCAGGGA GGCAAAGAGGCCAGGGGAATCTTCAAAGGCCCTGGGCTCATCCCAGCT AGGAGGC**[A/G]**GGCACAGTCATAACCCTAATCCAGTGAACTCAGCCCTC ATCCTGACTCTCATGGTATTCTGTCCCAGGGAGCCTCTTTCCAGCTTTCT TAGAAGCTTTAATGTCAGCACTTGCAGGGCCTTAGAAACTGCACGCTAC CTCTTCATTTCATACATGAGGAAACTGAGGCCCAGGGTGGACACAGGGC TGCCCAGCGAGTTA |

| SNP_ID | SEQUENCE |
|---|---|
| RS10156056 SEQ ID NO. 30 | ATTATAAAGCAAAGCACTAACCTCATAGAATACCTGAGTCAAGTTCCCTG TGTTCTCATTTTCTAGCCTCTTCTACCAGACACTATGAAAAATAACAGCC CCATCTCTCCAGAAAATCTTAGGAGATATAGGCGTGCTGAATTTAAGGT GTCTGTGGCACATGCAAGTGGATCAGCCACTGGGCTGTCCAGAATGCA AGA**[C/G]**AGAACTCAGAGTTGGGGACATAAACTTGGCAGTCATCTGTGTA AAAGAGAAAAGGTAGGTAAAGTCCCACAAGGATGGGTTGGCCTACAGAA GGCACAGAGAGAAGAGAGCCTGGTTTAGCATGGGCTACGATCAGAGTC CCTGGGTTCAAATCTTGGCTCCACCCATTTCTATCTGGTTGCTCTAGGG CATGTTACCTA |

Polymorphisms in linkage disequilibrium with a SNP of table 2 can be identified by by methods known in the art. For example, Develin and Risch (Genomics, 1995) provide guidance for determining the parameter delta (also referred to as the "r") as a standard measure of the disequilibrium. Gabriel *et al*. (Science, 2002) provides instructions for finding the maximal $r^2$ value in populations for disease gene mapping. Further, Carlson *et al.* (Am. J. Hum. Genet. (2003) disclose methods for selecting and analyzing polymorphisms based on linkage disequilibrium for disease gene association mapping. Stoyanovich and Pe'er (Bioinformatics, 2008) show that polymorphisms in linkage disequilibrium with indentified SNPs have virtually identical response profiles. Currently, several databases provide datasets that can be searched for polymorphisms in strong linkage disequilibrium, which can be accessed by the following addresses: http://1000.genomes.org, http://www.hapmap.org, http://www.broadinsitute.org/mpg/snap. An example workflow for determining SNPs linkage disequilibrium to a specific SNP is outlined in Uhr *et al*. (Neuron, 2008).

SNP in strong linkage disequilibrium as used herein means that the SNP is in linkage disequilibrium with an $r^2$ higher than 0.7 or higher than 0.8 in the tested population or an ethnically close reference population with the identified SNP.

In another embodiment, at least 20, optionally at least 25 or at least 30 SNPs selected from the group of table 2 are determined in step (a) and integrated by the prediction algorithm in step (b). For example, all intergenic SNPs of table 2 are determined in step (a) and integrated by the prediction algorithm in step (b). In another exemplary embodiment, all SNPs selected from the group of table 2 are determined in step (a)

and integrated by the prediction algorithm of step (b).

Typically, in step (a) of the method of predicting a treatment response to CRHR1 antagonists, the presence or absence of those SNPs is determined which were identified to be associated with values indicative for normal CRH activity or CRH overactivity and were thus considered when determining the prediction algorithm by machine-learning as described above.

In one embodiment of the method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, the method as described above may be accompanied by analyzing the rapid-eye-movement (REM) sleep, e.g. during night sleep of a patient in a sleep EEG.

In other embodiments, an increase in REM sleep may serve as a biomarker to identify patients who would benefit from treatment with a CRHR1 antagonist.

REM sleep typically comprises a characteristic coincidence of nearly complete muscle atonia, a waking-like pattern of brain oscillations and rapid eye movements (REMs). The amount of REMs during consecutive REM sleep episodes is usually increasing throughout the night. Single and short REMs with low amplitude can be characteristic for initial parts of REM sleep. The amount of REMs, in particular within the first REM sleep episode, can be of clinical relevance. Recent clinical and animal data supports the correlation of REM density with an increased CRH activity. For example, Kimura et al. (Mol. Psychiatry, 2010) showed that mice overexpressing CRH in the forebrain exhibit constantly increased rapid eye movement (REM) sleep compared to wildtype mice. In addition, it could be shown that treatment with the CRHR1 antagonist DMP696 could reverse the REM enhancement.

Further, the SNP analysis and REM density analysis as described herein may be combined for predicting the response of patients with depressive symptoms and/or anxiety symptoms to treatment with a CRHR1 antagonist. The REM analysis may be carried out before, concomitant or after the SNP analysis. For example, the REM

density analysis may be carried out on persons that where identified by the SNP analysis as CRH hyperdrive patients.

The recording of a "sleep-EEG" (also referred to "polysomatic recordings") may comprise electroencephalography (EEG), vertical and horizontal elecrooculography (EOG), electromyography (EMG) and/or electrocardiography (ECG). In EOG, muscle activities of right and left eye may be recorded by electrooculograms (one or typically two channels) in order to visualize the phasic components of REM sleep.

"REM analysis" or "analyzing the rapid-eye-movement (REM)" may refer to a method comprising recoding of muscle activities of right and left eye by EOG and then analyzing the electrooculogram. The recognition of REM in the electrooculogram may be done manually (for example by standard guidelines Rechtschaffen and Kales, 1968, Bethesda, MD: National Institute of Neurological Diseases and Blindness).

The invention is further described in the following example which is solely for the purpose of illustrating specific embodiments of the invention, and is also not to be construed as limiting the scope of the invention in any way.

**Example 1**

**Methods:**

Patients:

Patients with unipolar or bipolar depression admitted as in-patients to the Max Planck Institute of Psychiatry (MPI), Munich, Germany, for treatment of a depressive episode were included in the study. Patients were diagnosed by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Patients with bipolar disorder or depressive disorder due to a general medical or neurological condition were excluded, as were patients with a lifetime diagnosis of drug abuse and depressive symptoms secondary to alcohol or substance abuse or dependency. Ethnicity was recorded using a self-report sheet for

nationality, first language and ethnicity of the patient and of all four grandparents. All patients were Caucasian and part of the Munich-Antidepressant-Response-Signature (MARS) project (Hennings *et al.*, J Psychiatr Res., 2009) (www.mars-depression.de). They were treated with antidepressant medications according to doctor's choice. Severity of depressive symptoms was assessed at admission and at the time of the dex/CRH test by trained raters using the 17-item Hamilton Depression Rating Scale (HAM-D, Hamilton, J Neurol Neurosurg Psychiatry, 1960). 192 patients fulfilling the criteria for at least a moderate to severe depressive episode (HAM-D≥18) at both time points and who had been administered a dex/CRH test within 10 days of in-patients admission and had genome-wide SNP data were included in this analysis. The study was approved by the Ethics Committee of the Ludwig Maximilians University in Munich, Germany, and written informed consent was obtained from all subjects.

Dex/CRH test:

The dex/CRH test was administered as described in detail in Heuser *et al.* (J Psychiatr Res., 1994). In brief, subjects were pre-treated with 1.5 mg of dexamethasone per os at 11 pm. The following day, at 3 pm, 3.30 pm, 3.45 pm, 4 pm and 4.15 pm blood was drawn. An intravenous bolus of 100 µg of human CRH (Ferring, Kiel, Germany) was given at 3.02 pm. Plasma ACTH concentrations were assessed by an immunometric assay without extraction (Nichols Institute, San Juan Capistrano, California; USA). The neuroendocrine response to the dex/CRH test was analyzed using the total area under the curve (AUC) of the ACTH response.

SNP Genotyping:

After enrollment in the study 40 ml of EDTA blood was drawn from each patient. DNA was extracted from fresh blood using the Puregene® whole blood DNA-extraction kit (Gentra Systems Inc; MN). Genotyping was performed on Illumina Human 610k quad genotyping arrays (Illumina Inc., San Diego, USA) according to the manufacturer's standard protocols. The average call rate exceeded 99 %, with samples below 98 % being either retyped or excluded from the study. The reproducibility for samples genotyped twice was 99.99 % or better.

Data analysis:

To identify genetic predictors for the ACTH response to the dex/CRH test in patients with moderate to severe depression, the 192 patients were randomly split into a training (N = 96) and test set (N = 96). The demographic and clinical descriptors of these two samples are given in table 3.

**Table 3:**

Demographic and clinical description of the 192 patients in the trainings and test set.

| | training set | test set | p-value |
|---|---|---|---|
| | | | |
| N | 96 | 96 | |
| | | | |
| % female | 52,1 | 57,2 | n.s. |
| % bipolar (1 or 2) | 12,5 | 12,5 | n.s. |
| % with psychotic symptoms | 15,2 | 11,4 | n.s. |
| | | | |
| age (mean years (SD)) | 47,2 (14,2) | 51,3 (13,2) | 0,038 |
| BMI at admission (mean SD) | 24,9 (4,1) | 24,9 (4,3) | n.s. |
| age-on (mean years (SD)) | 34,72 (14,5) | 36,6 (15,9) | n.s. |
| number of previous episodes (mean N (SD)) | 3,2 (4,0) | 3,3 (4,7) | n.s. |
| depression severity at admission (mean HAMD-17 score (SD)) | 26,4 (4,4) | 27,7 (4,8) | 0,058 |
| depression severity at dex-crh test (mean HAMD-17 score (SD)) | 26,9 (5,0) | 28,5 (5,0) | 0,029 |
| | | | |
| | | | |
| Cortisol AUC (mean (SD)) | 3611,4 (3414) | 3688,6 (3491) | n.s. |
| ACTH AUC (mean (SD)) | 1246 (910) | 1482,8 (1319) | n.s. |
| days after admission when dex-CRH test was performed | 6,1 (2,2) | 5,9 (2,2) | n.s. |

After natural log transformation of the AUC of the ACTH response in the dex/CRH test, patients were dichotomized into high vs. low responders. For the ACTH AUC the cut-off was ln ACTH AUC > 7.0. This placed 46.4% (89 out of a total of 192 individuals) in the high responder class. See the corresponding histogram in Figure 1.

Using an additive genetic model and a logistic regression with sex and age as covariates in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/), the association of all SNPs with a MAF > 0.05 were tested on the 610k arrays with the dichotomized response for cortisol and ACTH in the dex/CRH test in the training set. The top 30 associated SNPs were then used to predict either ACTH or cortisol response status in the test set using a "Probabilistic Neural Network und General Regression Neural Network" approach (implementation DTREG 10.3.3 www.dtreg.com). All values were derived from a 20 fold cross validation.

**Results:**

The top 30 association with ACTH response status are given in table 4. Association p-values ranged from 5.0 e-5 to 2.3 e-4 for the ACTH response.

The genotypes for the 30 SNPs each were then used to predict ACTH response status in the second, independent test cohort (subgroup of the test set).

**Table 4**: List of 30 SNPs used to predict ACTH AUC in the second test cohort.

| SNP | Chromosome | Coordinate_HG18 | P-value training | GeneVariant | GeneName |
|---|---|---|---|---|---|
| | | | | | |
| rs6437726 | chr3 | 108321446 | 5.037e-005 | INTERGENIC | N/A |
| rs1986684 | chr11 | 110629697 | 5.287e-005 | UPSTREAM | N/A |
| rs7380830 | chr5 | 66022641 | 5.459e-005 | INTRONIC | ENSG0000019656 |
| rs3903768 | chr13 | 49294756 | 6.811e-005 | INTERGENIC | N/A |
| rs7325978 | chr13 | 71960761 | 8.206e-005 | INTERGENIC | N/A |
| rs13585 | chr22 | 45131843 | 0.0001016 | REGULATORY_REGION,3PRIME_UTR | TRMU |
| rs9368373 | chr6 | 22024631 | 0.0001063 | INTERGENIC | N/A |
| rs10935354 | chr3 | 141026326 | 0.0001073 | INTERGENIC | N/A |
| rs8095703 | chr18 | 11041081 | 0.0001183 | INTERGENIC | N/A |
| rs10206851 | chr2 | 5381477 | 0.0001267 | INTERGENIC | N/A |
| rs9542977 | chr13 | 71958236 | 0.0001499 | INTERGENIC | N/A |
| rs4942879 | chr13 | 49314940 | 0.0001537 | INTERGENIC | N/A |
| rs9542954 | chr13 | 71918308 | 0.0001643 | INTERGENIC | N/A |
| rs1593478 | chr18 | 2292023 | 0.0001663 | INTERGENIC | N/A |
| rs9542951 | chr13 | 71913959 | 0.0001664 | INTERGENIC | N/A |
| rs2188534 | chr7 | 111837550 | 0.0001823 | INTERGENIC | N/A |
| rs12524124 | chr6 | 22051921 | 0.000185 | INTERGENIC | N/A |
| rs4352629 | chr5 | 87792577 | 0.0001985 | INTERGENIC | N/A |
| rs7448716 | chr5 | 87788451 | 0.0001985 | INTERGENIC | N/A |
| rs11873533 | chr18 | 3732713 | 0.0002107 | INTRONIC | DLGAP1 |
| rs10062658 | chr5 | 102881920 | 0.0002216 | INTERGENIC | N/A |
| rs12547917 | chr8 | 142306580 | 0.0002282 | INTRONIC | SLC45A4 |
| rs1038268 | chr9 | 31967623 | 0.000229 | INTERGENIC | N/A |
| rs2375811 | chr9 | 31979998 | 0.000229 | INTERGENIC | N/A |
| rs1352671 | chr9 | 32033985 | 0.000229 | INTERGENIC | N/A |
| rs364331 | chr9 | 32039631 | 0.000229 | INTERGENIC | N/A |
| rs1924949 | chr13 | 71975473 | 0.0002323 | INTERGENIC | N/A |
| rs11025990 | chr11 | 21218608 | 0.0002323 | INTRONIC | NELL1 |
| rs3758562 | chr10 | 72032086 | 0.0002369 | INTRONIC | PRF1 |
| rs10156056 | chr7 | 22720613 | 0.0002394 | INTERGENIC | N/A |

The results of the prediction in the test set are summarized below:

For the prediction of the dichotomized ACTH response status in the dex/CRH the following prediction values were achieved:

**ACTH:**

Accuracy = 85.33%

Sensitivity = 87.18%

Specificity = 83.33%

Geometric mean of sensitivity and specificity = 85.23%

Positive Predictive Value (PPV) = 85.00%

Negative Predictive Value (NPV) = 85.71%

Geometric mean of PPV and NPV = 85.36%

Precision = 85.00%

Recall = 87.18%

F-Measure = 0.8608

Area under ROC curve (AUC) = 0.851852

Using genome-wide SNP association data for the ACTH response in the dex/CRH test, a subset of 30 SNPs could be identified that allowed an accurate, sensitive and specific prediction of these phenotypes in independent sets of patients. Increased ACTH secretion in this test has been linked to an increase in central CRH/CRHR1 function. Although environmental, pharmacological and disease state-dependent factors have previously been described to influence the endocrine response to this test in depressed patients (Ising *et al.*, Neuropsychopharmacol Biol Psychiatry, 2005; Heim *et al.* Biol Psychiatry, 2008; Kunzel *et al.* Neuropsychopharmacology, 2003), it has now been shown that genetic polymorphisms alone are strong predictors.

Patients with depression or anxiety disorders, classified into the high ACTH response group according to the genotypes of the presented 30 SNPs described in this example will be more likely to respond to CRHR1 antagonist treatment. This allows an

enrichment of such patients for CRHR1 antagonist treatment studies who will most likely respond to this specific treatment.

**Example 2:**

Sleep disturbances, such as decreased slow-wave sleep, increased sleep fragmentation and rapid-eye-movement sleep (REMS) disinhibition, are cardinal symptoms of major depression in humans. This study aims to identify those patients where a central CRH hyperdrive plays a causal role and which would therefore respond favourably to a CRHR1 antagonist. To test the relationship between a central CRH-overexpression and REM-disinhibition in particular, transgenic mouse models where CRH is overexpressed as a result of genetic engineering were employed.

Many animal models of depression share increases in REM-sleeps (REMS) as a common feature. Therefore, increased REMS in animals should reflect REMS-disinhibitions in humans. Mice with CNS-specific CRH-overexpression strikingly share the characteristic increases in REMS. As such, an increase in REMS indicates a central hypersecretion of CRH and may serve as a biomarker to identify those patients who would benefit from treatment with a CRHR1 antagonist.

Experiments were conducted with two different mouse lines of excessive central CRH secretion and their respective control littermates (CL). Mice of the CRH-$COE^{CNS}$ line are characterised by CRH-overexpression within the whole CNS, whereas mice of the Cor26 CRH line display a CRH-overexpression specific to CRH-ergic neurons of the CNS. Three different CRHR1 antagonists were tested. While DMP-696 (bicyclic) and CP-316,311 (monocyclic) are class I CRH-R1 antagonists, SSR125543A (long off-rate, typical slow-tight binding inhibitor) belongs to class II CRH-R1 antagonists. DMP-696 and SSR125543A were applied to CRH-$COE^{CNS}$ mice ($n_{DMP696}$= 6/6 COE/CL; $n_{SSR125543}$= 6/5 COE/CL), while CP-316,311 was tested in Cor26 CRH mice ($n_{CP316.311}$= 5/3 Cor26/CL). In all cases, animals were left to recover from EEG/EMG-electrode implantation for two weeks, after which two days of baseline recording were initiated. Treatment with CRH-R1

antagonist or respective vehicle control commenced thereafter for five consecutive days. Antagonists were applied through the drinking water at a daily dose of 50mg/kg body weight. EEG and EMG recordings were manually scored as wake, non-REMS (NREMS), and REMS in four second epochs by an experienced evaluator.

As previously shown, CRH-COE$^{CNS}$ mice display significantly higher REMS activity under baseline condition as compared to controls. Chronic DMP-696 (50mg/kg/d DMP-696) treatment entails only a mild suppression of REMS in CL mice. However, DMP-696-treated CRH-COE$^{CNS}$ mice show a significant decrease in REMS activity beginning with treatment day two ($P<0.05$). The strongest suppression of REMS activity in CRH-COE$^{CNS}$ animals could be observed on treatment day three (Figure 2).

Comparable to DMP696 treatment, oral application of SSR125543A (50mg/kg/d) affected REMS levels in CRH-overexpressing mice. No effects of SSR125543 on REMS activity in control animals could be detected. In contrast, a significant suppression of REMS could be observed beginning with day two in CRH-overexpressing animals ($P\leq0.035$). Similar to DMP696 treatment, REMS suppression in CRH-COE$^{CNS}$ mice never exceeded baseline REMS-levels of CL (Figure 3).

Application of CP-316,311 (Pfizer) in the Cor26 CRH mouse line showed no significant effect on REMS levels in CL animals (data not shown). Similarly, in CRH-overexpressing Cor26 CRH mice suppression in REMS apparently seemed weak. However, comparison of the area under the curve (AUC) within the light period of baseline and treatment day three showed a significant decrease ($P=0.006$) of REMS levels after CP-316,311 application (Figure 4).

CRH is one of the major drivers of the stress response in the brain. Hyperactivity of the CRH system seems to be responsible for cognitive impairments, emotional responses, and behavioural changes which are typical for depression. One of those

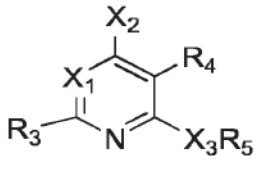
behavioural changes are sleep disturbances exemplified by REMS disinhibition. The link between CRH-overexpression and REMS level increases is evidenced by the mouse lines used in these experiments. Since CRH-overexpression in the Cor26 CRH mouse line is limited to CRH-ergic neurons, the net increase of CRH is lower when compared to the whole brain overexpression in CRH-COE$^{CNS}$ mice. As a result, the phenotype of increased REMS levels was less profound in Cor26 CRH mice as compared to CRH-COE$^{CNS}$ animals.

The main finding of this study is that the normalization of CRH-elicited sleep-EEG disturbances is striking when (1) different chemical classes of CRHR1 antagonists are used and (2) different animal models for CRH-induced sleep-EEG changes that are typical for human depression are employed. REMS disinhibition is indicative of a central CRH dysfuntion (i.e. hyperactivity) and as such may serve as a biomarker for the identification of depressed patients where depression is caused by central CRH-hyperdrive. Normalization of the sleep pattern by application of different CRHR1 antagonists could be shown in all of our experiments, employing different classes of CRHR1 receptors and different animal models overexpressing centrally CRH.

## Claims

1. Corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

2. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

$X_1$ is $-CR_6$ or N;

$X_2$ is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

$X_3$ is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{11}R_{12})$, wherein $R_{11}$ and $R_{12}$ are each, independently, hydrogen, trifluoromethyl or methyl, or one of $R_{11}$ and $R_{12}$ is cyano and the other is hydrogen or methyl, or

$X_3$ is N and $X_3$ and $R_4$ form a 5-membered ring substituted at $X_3$ with $R_5$;

$R_1$ is $C_1\text{-}C_6$ alkyl which may optionally be substituted with one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $CF_3$, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-O\text{-}CO\text{-}(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}NH(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_2$ alkyl)$(C_1\text{-}C_4$ alkyl), $-S(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_4$ alkyl)$CO(C_1\text{-}C_4$ alkyl), $-NHCO(C_1\text{-}C_4$ alkyl), $-COO(C_1\text{-}C_4$ alkyl), $-CONH(C_1\text{-}C_4$ alkyl), $-CON(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), CN, $NO_2$, $-SO(C_1\text{-}C_4$ alkyl) and $-SO_2(C_1\text{-}C_4$ alkyl), and

wherein said $C_1$-$C_6$ alkyl and the ($C_1$-$C_4$) alkyl moieties in the foregoing $R_7$ groups may optionally contain one carbon-carbon double or triple bond;

$R_2$ is $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ alkoxyalkyl,

aryl or -($C_1$-$C_4$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –($C_1$-$C_6$ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -($C_1$-$C_6$ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-$R_8$ wherein $R_8$ is hydrogen or $C_1$-$C_4$ alkyl;

and wherein each of the foregoing $R_2$ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl, or with one substituent selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), CN, $NO_2$, -SO($C_1$-$C_4$ alkyl), and -$SO_2$($C_1$-$C_4$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl and/or the $C_1$-$C_4$ alkylene moiety of said -($C_1$-$C_4$ alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -$NR_1R_2$ or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

$R_3$ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, $OCF_3$, methylthio, methylsulfonyl, $CH_2OH$, or $CH_2OCH_3$;

$R_4$ is hydrogen, $C_1$-$C_4$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_4$ alkoxy, trifluoromethoxy,

-$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH_2$OCF3, $CF_3$, amino, nitro, -NH($C_1$-$C_4$ alkyl), -N($CH_3$)$_2$, -NHCO$CH_3$ -NHCONH$CH_3$, -$SO_n$($C_1$-$C_4$ alkyl) wherein n is 0, 1 or 2, hydroxy, -CO($C_1$-$C_4$ alkyl), -CHO, cyano or -COO($C_1$-$C_4$

alkyl) wherein said $C_1$-$C_4$ alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -$NH(C_1$-$C_2$ alkyl), -$N(C_1$-$C_2$ alkyl)$_2$, -$COO(C_1$-$C_4$ alkyl), -$CO(C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, chloro, cyano and nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups $R_5$ is substituted with from one to three substituents independently selected from fluoro, chloro, $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, ($C_1$-$C_6$ alkyl)O($C_1$-$C_6$)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -$COO(C_1$-$C_4$ alkyl), -$CO(C_1$-$C_4$ alkyl), -$SO_2NH(C_1$-$C_4$ alkyl), -$SO_2N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -$SO_2NH_2$, -$NHSO_2(C_1$-$C_4$ alkyl), -$S(C_1$-$C_6$ alkyl) and $SO_2(C_1$-$C_6$ alkyl), and wherein the $C_1$-$C_4$ alkyl and the $C_1$-$C_6$ alkyl moieties of the foregoing $R_5$ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

$R_6$ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -$O(C_1$-$C_4$ alkyl), -$C(O)(C_1$-$C_4$ alkyl), -$C(O)O(C_1$-$C_4$ alkyl), -$OCF_3$, $CF_3$, -$CH_2OH$, -$CH_2OCH_3$ or -$CH_2OCH_2CH_3$;

$R_9$ is hydrogen, hydroxy, fluoro, or methoxy;

$R_{10}$ is hydrogen or $C_1$-$C_4$ alkyl.

3. CRHR1 antagonist for use according to claim 2, wherein
$X_1$ is $–CR_6$.

4. CRHR1 antagonist for use according to claim 3, wherein $X_1$ is CH.

5. CRHR1 antagonist for use according to any of claims 2 to 4, wherein the 5- to 8-membered ring formed by $-NR_1R_2$ or $–CR_1R_2R_9$ is substituted with at least one substituent selected from $C_1$-$C_4$ alkyl or
with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or $SO_2$ and one to four carbon atoms may optionally be replaced by nitrogen.

6. CRHR1 antagonist for use according to any of claims 2 to 4, wherein
$X_2$ is $–NHCHR_1R_2$, $–OCHR_1R_2$ or $-NR_1R_2$.

7. CRHR1 antagonist for use according to claim 6, wherein
$–NHCHR_1R_2$ is $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein $R_1$ is ethyl and $R_2$ is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl,
or
$-NR_1R_2$ is $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$
or
$–OCHR_1R_2$ is $–OCH(CH_2CH_3)_2$, $–OCH(CH_2CH_3)CH_3$, $–OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $–OCH(CH_2CH_3)(CH_2OCH_3)$.

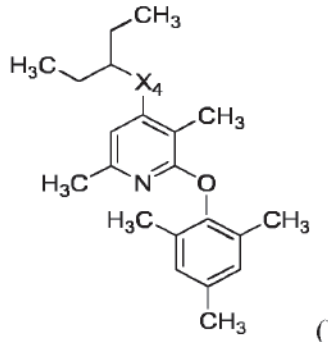
8. CRHR1 antagonist for use according to any of claims 2 to 7, wherein
$R_3$ and $R_4$ are methyl.

9. CRHR1 antagonist for use according to any of claims 2 to 8, wherein

$X_3$ is O.

10. CRHR1 antagonist for use according to any of claims 2 to 9, wherein $R_5$ is phenyl substituted with from one to three substituent(s) independently selected from the group $CH_3$, $CH_2CH_3$, $OCH_3$, Cl, F, $CF_3$.

11. CRHR1 antagonist for use according to any of claims 1 to 10, wherein the CRHR1 antagonist is a compound of the formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
$X_4$ is O or NH.

12. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a class I CRHR1 antagonist.

13. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a class II CRHR1 antagonist.

14. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965,

SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

15. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is DMP-696.

16. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is CP-316,311.

17. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is SSR125543A.

18. CRHR1 antagonist for use according to any of the preceding claims, wherein CRH overactivity is detected by determining the status of one or more markers indicative for CRH overactivity.

19. CRHR1 antagonist for use according to claim 18, wherein the marker is selected from the group consisting of a biomarker, a set of biomarkers and a clinical marker.

20. CRHR1 antagonist for use according to any of claim 19, wherein the biomarker or the set of biomarkers is obtained by a genome-wide screening for single nucleotide polymorphisms in patients with depressive and/or anxiety symptoms.

21. CRHR1 antagonist for use according to claims 19 or 20, wherein the biomarker or the set of biomarkers is selected from the group comprising:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,

- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562, and/or
- SNP rs10156056.

22. CRHR1 antagonist for use according to any of claims 19 to 21, wherein the biomarker or the set of biomarkers constituting a marker for CRH activity is selected from one or more biomarkers from the group comprising:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G, and/or
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

23. CRHR1 antagonist for use according to any of claims 19 to 22, wherein the set of biomarkers comprises at least 15, at least 20 or at least 25 of the biomarkers as defined in claims 21 or 22.

24. CRHR1 antagonist for use according to any of claims 19 to 23, wherein the set of biomarkers consists of the biomarkers as defined in claims 21 or 22.

25. CRHR1 antagonist for use according to any of claims 18 or 24, wherein the biomarker is REM density.

26. CRHR1 antagonist for use according to any of claims 18 or 25, wherein the marker is a combination of a biomarker or set of biomarkers as defined in any of claims 20 to 24 with the biomarker REM density.

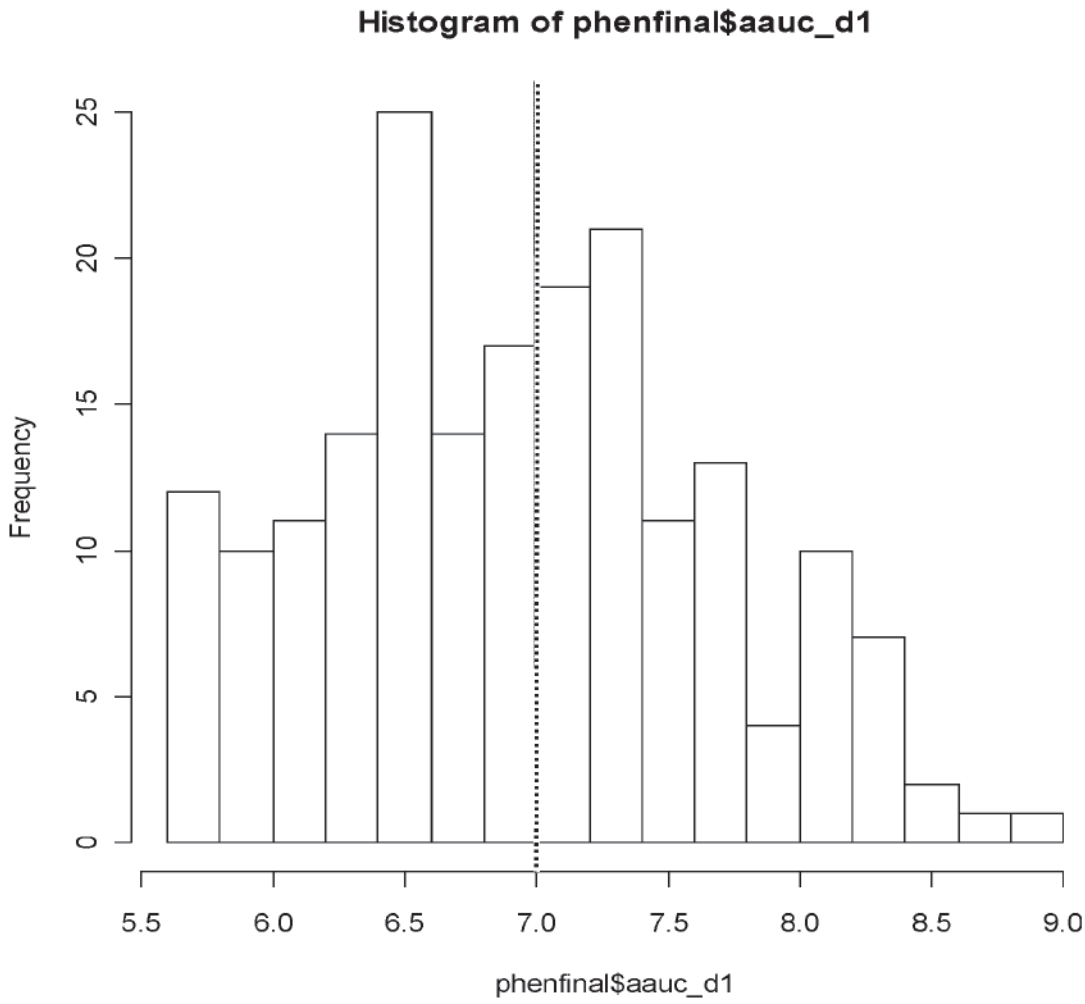

Histogram of phenfinal$aauc_d1
Frequency
0
5
10
15
20
25
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
phenfinal$aauc_d1

Fig. 1

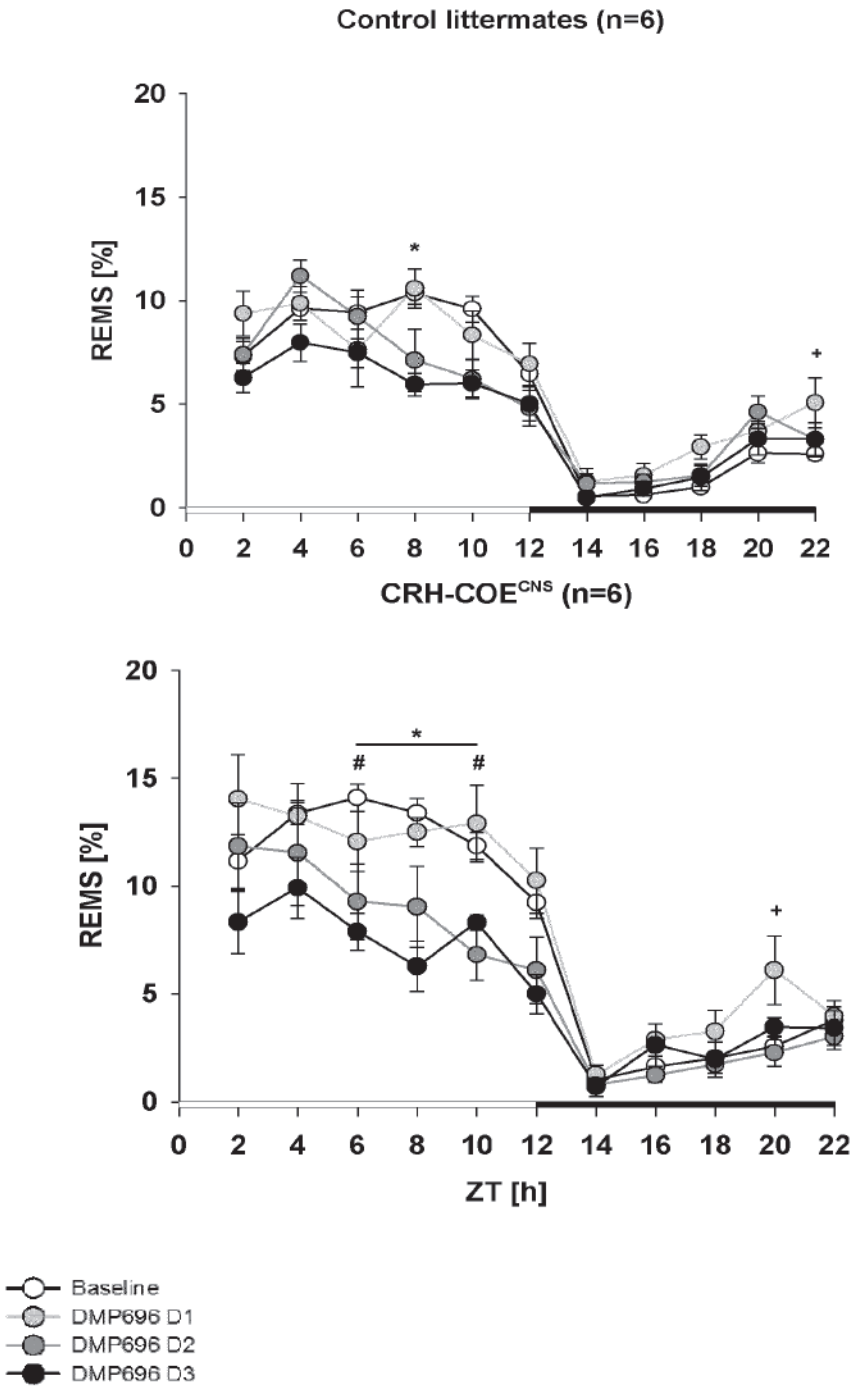

Control littermates (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
+
CRH-COE^CNS (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
#
#
+
ZT [h]
Baseline
DMP696 D1
DMP696 D2
DMP696 D3

Fig. 2

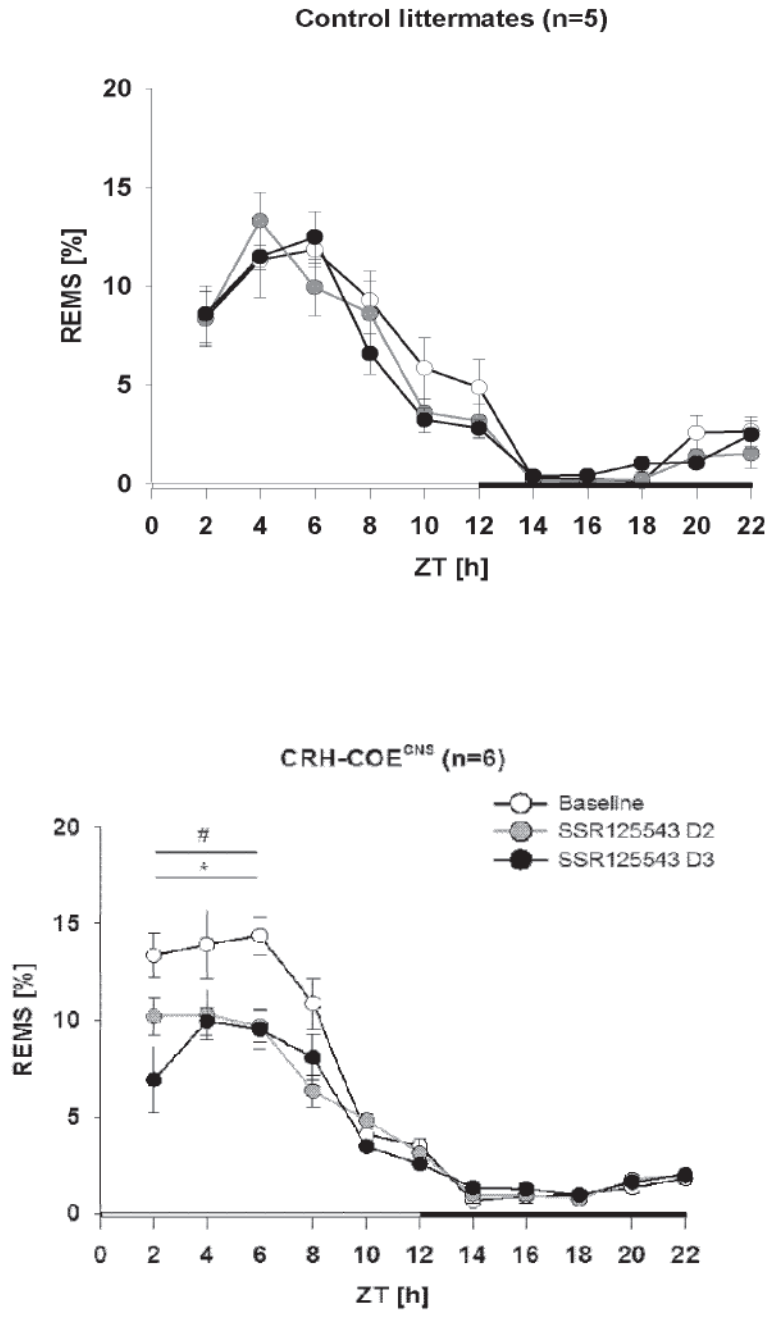

Control littermates (n=5)
REMS [%]
ZT [h]
CRH-COE^CNS (n=6)
Baseline
SSR125543 D2
SSR125543 D3
#
*
REMS [%]
ZT [h]

Fig. 3

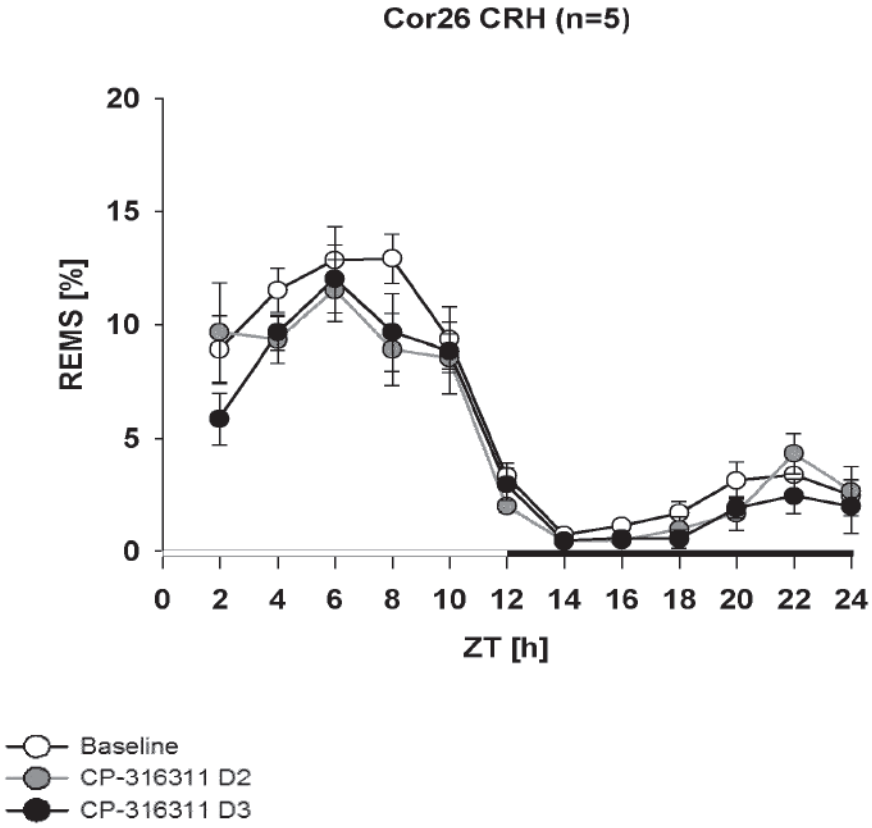

Cor26 CRH (n=5)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24
ZT [h]
Baseline
CP-316311 D2
CP-316311 D3

Fig. 4

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# GRANT LETTER

| APPLICATION # | DECISION DATE | DECISION ON PETITION # | ATTORNEY DOCKET NUMBER |
|---|---|---|---|
| 18/307,718 | 07/12/2024 | 37 CFR 1.313(c)(2) | 50535-709.307 |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

**In re Application of Alexis HOWERTON**

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed July 12, 2024 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

**Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.**

The application is being referred to Technology Center AU for processing of the request for continuing examination under 37 CFR 1.114 .

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions

UNITED STATES PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2)

| APPLICATION # | ATTORNEY DOCKET # | FILING DATE |
|---|---|---|
| 18307718 | 50535-709.307 | 04/26/2023 |

Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Application Information

| | | | |
|---|---|---|---|
| CONFIRMATION # | 9067 | FILING DATE | 04/26/2023 |
| ART UNIT | 1612 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| EXAMINER | CELESTE RONEY | | |

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

**A grantable petition requires the following items:**

(1) Petition fee; and
(2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination - RCE request, submission, and fee are attached

## Applicant claims the following entity status

Regular Undiscounted

## Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:
An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

| Signature | Name | Registration # |
|---|---|---|
| /Kaia R. Parenti/ | Kaia Parenti | 81050 |

# Bibliographic data

| | |
|---|---|
| **Title:** | Selective androgen receptor modulators, analogs and derivatives thereof and uses thereof |
| **Pub/Pat no:** | CN101516835A |
| **Pub/Issue Date:** | 2009-08-26 |
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| **Applicant(s):** | OSURF OHIO STATE UNIVERSITY RE[US] |
| **Classification:** | C07C255/00AI; C07D207/00AI |
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## Abstract of CN101516835A

This invention provides new compounds and uses thereof in treating a variety of diseases or conditions in a subject, including,inter alia, prostate cancer, muscle wasting diseases and/or disorders or a bone-related diseases and/or disorders.

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权利要求书 32 页 说明书 162 页 附图 19 页

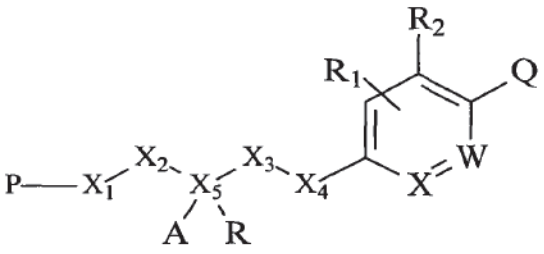
[54] 发明名称

选择性雄激素受体调节剂、它们的类似物和衍生物以及它们的用途

[57] 摘要

本发明提供新型化合物以及它们在治疗个体的各种疾病或病症中的用途，所述疾病或病症尤其包括前列腺癌、肌萎缩疾病和/或病症、或骨相关疾病和/或病症。

1. 化合物，其由式 I 的结构表示：



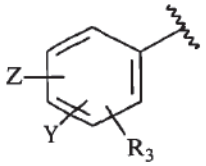
I

其中

X 是 C 或 N；W 是 C 或 N；

$X_1$ 是 N、NH、N($C_{1-4}$ 烷基)、NAc、NCOOH 或键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

P 是 H 或式 II：



II

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；或者 $X_2$ 和 $R_3$ 与 $X_2$ 所连接的 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_2$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

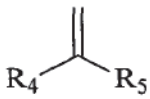
$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)、键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_3$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和

的、取代的或未取代的 3-6 元环；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；或者 $X_4$ 和 $X_5$ 与 $X_4$ 和 $X_5$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

$X_5$ 是碳或者 $X_5$ 和 $X_1$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_2$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_3$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_4$ 与 $X_5$ 和 $X_4$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

A 不存在，或是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；或者 A 和 R 形成式 III 所表示的双键：




III

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、卤化物、$CF_3$、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、O($C_{1-4}$ 烷基)或 O($C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、$NH_2$、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基

或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN、$NO_2$；或者 $R_3$ 和 $X_2$ 与 $R_3$ 所连接的苯环和 $X_2$ 所连接的 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

R'是 $NH_2$、OH 或 $CH_3$；

$R_4$ 和 $R_5$ 独立地是 H、$CH_3$、卤化物、OH、$C_{1-4}$ 烷基、$C_{1-6}$ 环烷基、卤代($C_{1-4}$ 烷基)、苯基、芳基、$C_{4-8}$ 杂环烷基或羟基($C_{1-4}$ 烷基)；

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

其中

如果 P 是式 II，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，$X_3$ 是 $CH_2$，R 是 OH 并且 A 是烷基或卤代烷基，那么 $X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$N[CH_2CH_2N(CH_3)_2]$、$P(O)(C_{1-4}$ 烷基)或 $N(O)[CH_2CH_2N(CH_3)_2]$；

或者

如果 P 是式 II，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，$X_3$ 是 $CH_2$，R 是 OH 或 OAlk 并且 $X_4$ 是 O、S、NH、S、SO、$SO_2$ 或亚烷基，那么 A 是 CN、$CH_2OH$、$CH_2O(C_{1-4}$ 烷基)、$CH_2O(C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$ 烷基)、C(O)R'、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

或者

如果 P 是苯基，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH 并且 A 是 COOH，$X_3$ 是键，$X_4$ 是 $CH_2$，$R_1$、$R_2$ 是 H，那么 Q 不是 H；

或者

如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

或者

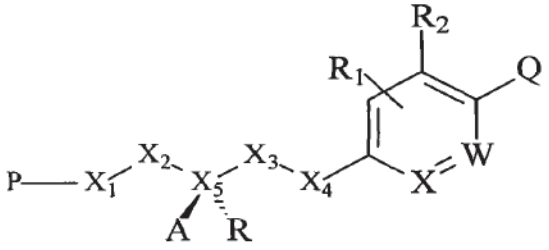
如果 P 是 H，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$ 并且 $X_4$ 是键或 $CH_2$，$R_1$ 和 $R_2$ 是 H，那么 Q 不是 H 或卤素；

或者

如果 P 是式 II，$R_3$ 是 H，X 和 W 是 C，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的

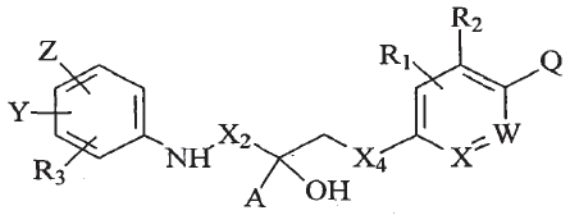
$X_2$ 一起形成噁唑烷二酮，R 是烷基，$X_3$ 是 $CH_2$ 并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

2. 权利要求 1 的化合物，其由以下结构表示：



。

3. 权利要求 1 的化合物，其中所述化合物由式 IV 的结构表示：



IV

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、$CH(NH_2)$、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

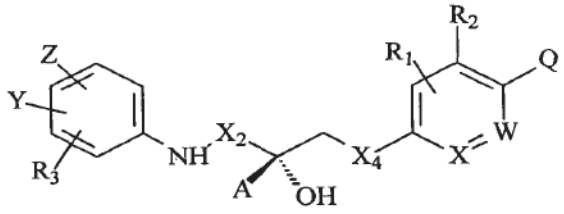
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

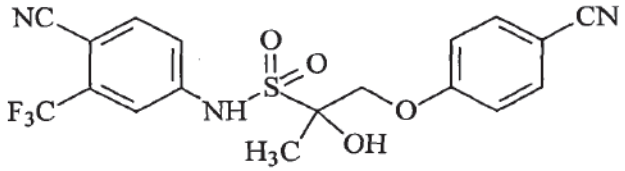
$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

4. 权利要求 3 的化合物，其由以下结构表示：



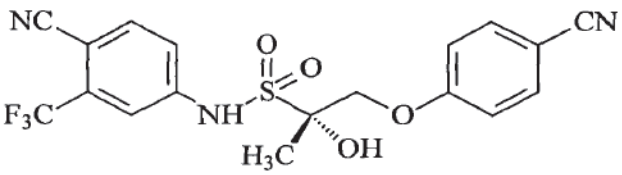

。

5. 权利要求 2 的化合物，其中所述化合物由式 V 的结构表示：



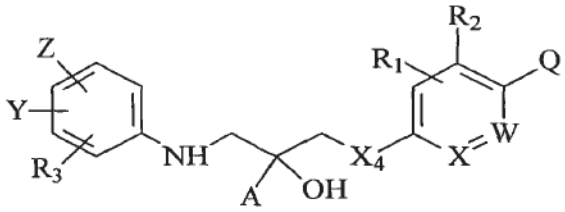

V 。

6. 权利要求 5 的化合物，其由以下结构表示：



。

7. 权利要求 2 的化合物，其中所述化合物由式 VI 的结构表示：



VI

其中

X 是 C 或 N； W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=CHCH$_2$N(CH$_3$)$_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[CH$_2$CH$_2$N(CH$_3$)$_2$]、C[=CHCH$_2$N(CH$_3$)$_2$]、PO($C_{1-4}$ 烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、O($C_{1-4}$ 烷基)或 O($C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

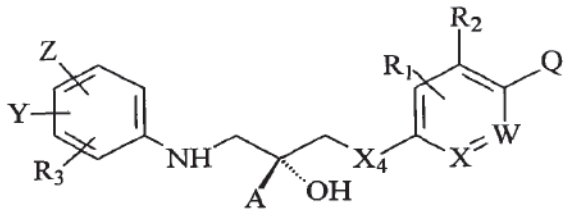
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

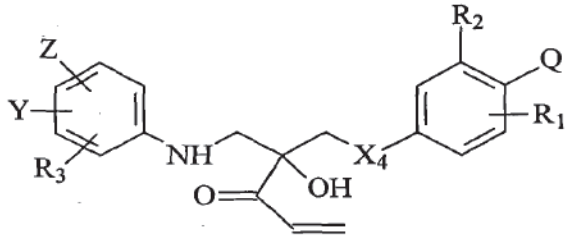
$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

8. 权利要求 7 的化合物，其由以下结构表示：



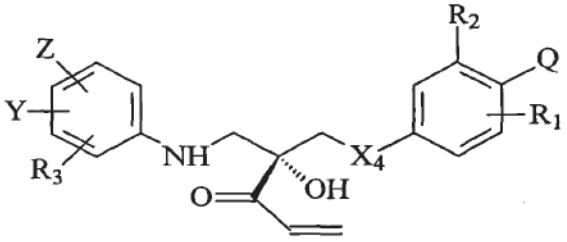
。

9. 权利要求 7 的化合物，其中所述化合物由式 VII 的结构表示：



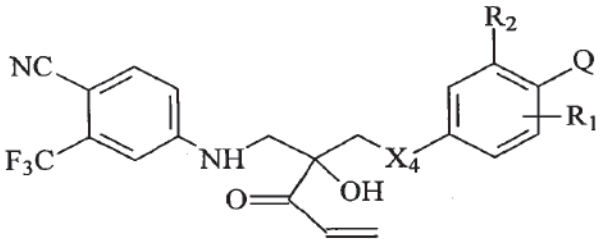
VII 。

10. 权利要求 9 的化合物，其由以下结构表示：



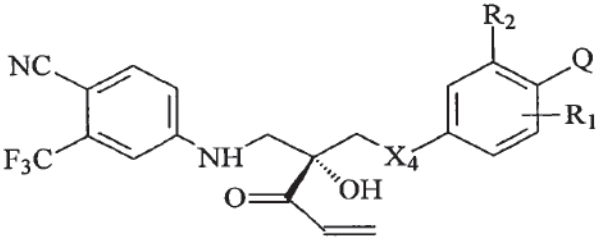
。

11. 权利要求 9 的化合物，其中所述化合物由式 X 的结构表示：



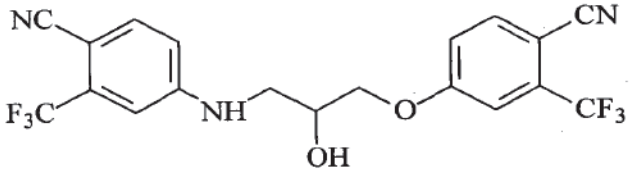
VIII 。

12. 权利要求 11 的化合物，其由以下结构表示：



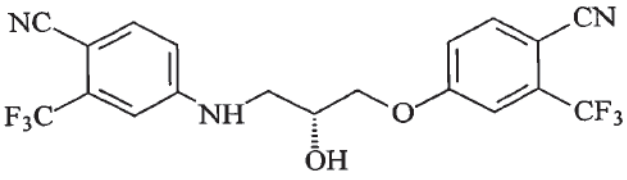
。

13. 权利要求 7 的化合物，其中所述化合物由式 IX 的结构表示：



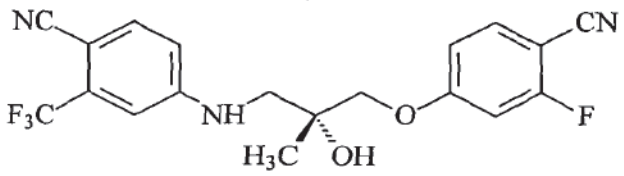
IX 。

14. 权利要求 13 的化合物，其由以下结构表示：



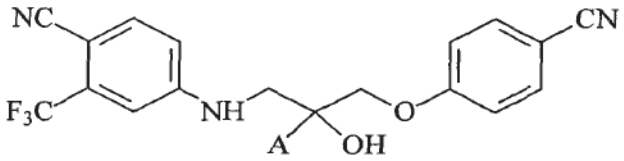
。

15. 权利要求 7 的化合物，其中所述化合物由式 X 的结构表示：



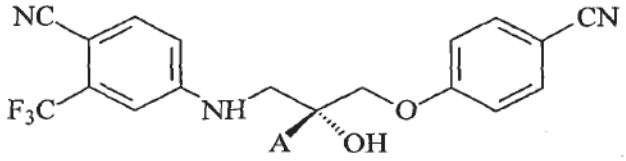
X 。

16. 权利要求 7 的化合物，其中所述化合物由式 X 的结构表示：



XI 。

17. 权利要求 16 的化合物，其由以下结构表示：



。

18. 权利要求 15 的化合物，其中 A 是 $CH_2OH$。

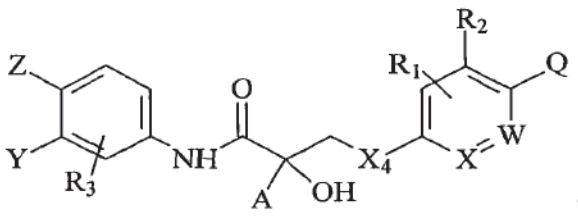
19. 权利要求 17 的化合物，其中 A 是 $CH_2OMe$。

20. 权利要求 17 的化合物，其中 A 是 $CF_3$。

21. 权利要求 17 的化合物，其中 A 是 $CH_3$。

22. 权利要求 17 的化合物，其中 A 是 CN。

23. 权利要求 1 的化合物，其中所述化合物由式 XII 的结构表示：



XII

其中

X 是 C 或 N；W 是 C 或 N；

$X_4$ 是 O、S、SO、S(O)[=CHCH$_2$N(CH$_3$)$_2$]、SO$_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[CH$_2$CH$_2$N(CH$_3$)$_2$]、C[=CHCH$_2$N(CH$_3$)$_2$]、PO($C_{1-4}$ 烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]或键；

A 是 CN、CH$_2$OH、CH$_2$O($C_{1-4}$ 烷基)、CH$_2$O($C_{1-4}$ 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、CH$_2$OR'CH$_2$C(O)CH=CH$_2$ 或 C(O)CH=CH$_2$；

Z 是 H、CN、NO$_2$、NHC(O)CH$_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、CF$_3$、CN、NO$_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO$_2$、CF$_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、C(O)CH$_2$NH$_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、C(O)NH$_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、CH$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO($C_{1-4}$ 烷基)、NHSO$_2$($C_{1-4}$ 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$($C_{4-8}$ 环烷基)]、O-[CH$_2$CH$_2$($C_{4-8}$ 杂环烷基)]或 O-[CH$_2$CH$_2$N(CH$_3$)$_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、(CH$_2$)$_2$-O-对氰基苯基、CH$_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 NO$_2$；

R'是 NH$_2$、OH 或 CH$_3$；并且

$R_6$ 是 CN、NO$_2$、NHC(O)CH$_3$ 或卤化物。

24. 权利要求 23 的化合物，其中 $X_4$ 是 O。

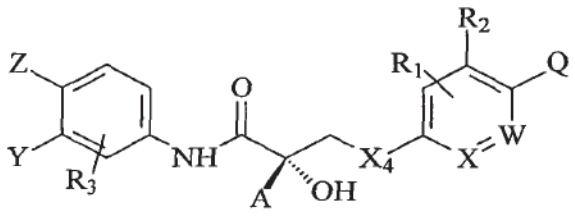
25. 权利要求 24 的化合物，其中 A 是 CH$_2$OH。

26. 权利要求 24 的化合物，其中 A 是 CN。

27. 权利要求 23 的化合物，其中 Q 是 CN，$R_1$ 和 $R_2$ 是 H。

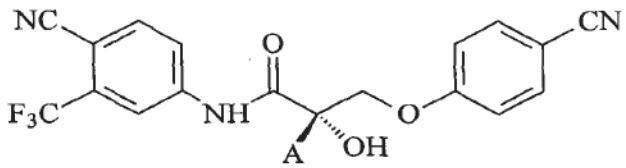
28. 权利要求 23 的化合物，其中 Q 是 CN，Z 是 CN，Y 是 $CF_3$，并且 $R_1$、$R_2$ 和 $R_3$ 是 H。

29. 权利要求 23 的化合物，其由以下结构表示：



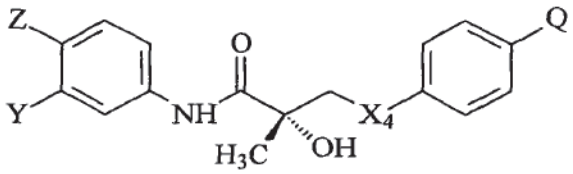

。

30. 权利要求 23 的化合物，其中所述化合物由式 XIII 的结构表示：




XIII 。

31. 权利要求 1 的化合物，其中所述化合物由式 XVII 的结构表示：




XVII

其中

$X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基）、$N[CH_2CH_2N(CH_3)_2]$、

NO[$CH_2CH_2N(CH_3)_2$]；

Q 是 H、CN、OH、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；并且

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br。

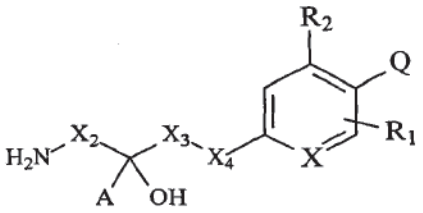
32. 权利要求 31 的化合物，其中 Q 是 F。

33. 权利要求 31 的化合物，其中 Q 是 CN。

34. 权利要求 31 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

35. 权利要求 31 的化合物，其中 Q 是 CN，Z 是 CN 且 Y 是 $CF_3$。

36. 权利要求 1 的化合物，其中所述化合物由式 XIX 的结构表示：




XIX

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、$CH(C_{1-4}$ 烷基)、$CH(NH_2)$、CH(OH)、$CH(C_{1-4}$ 卤代烷基)、键；

$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)或键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、$PO(C_{1-4}$

烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O(C_{1-4}$烷基)、$CH_2O(C_{1-4}$酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$烷基)、$C(O)N(C_{1-4}$烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$烷基)、$NHC(O)NH(C_{1-4}$烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$烷基)、$NHSO_2(C_{1-4}$烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$环烷基)]、$O-[CH_2CH_2(C_{4-8}$杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

其中

如果 X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$，并且 $X_4$ 是键或 $CH_2$，$R_1$ 和 $R_2$ 是 H，那么 Q 不是 H 或卤素。

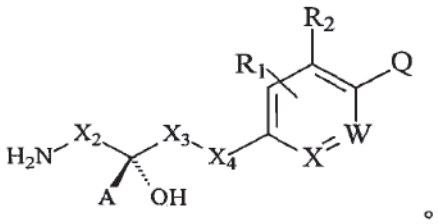
37. 权利要求 36 的化合物，其中 $X_2$ 是 $CH_2$。

38. 权利要求 36 的化合物，其中 $X_2$ 是 C(O)。

39. 权利要求 36 的化合物，其中 $X_3$ 是 $CH_2$。

40. 权利要求 36 的化合物，其中 $X_4$ 是 O。

41. 权利要求 36 的化合物，其由以下结构表示：

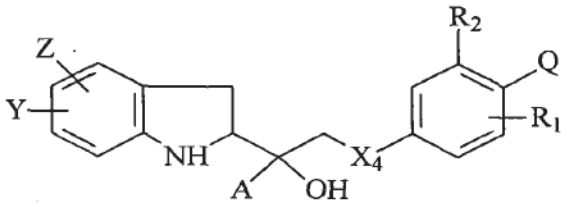


。

42. 权利要求 1 的化合物，其中 P 是式 II，并且 $X_2$ 和 $X_3$ 与 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。

43. 权利要求 42 的化合物，其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、吡咯、吗啉、哌啶-4-酮或哌啶。

44. 权利要求 42 的化合物，其中所述化合物由式 XX 的结构表示：



XX

其中

$X_4$ 是 O、S、SO、C(O)、S(O)[=CHCH$_2$N(CH$_3$)$_2$]、SO$_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[CH$_2$CH$_2$N(CH$_3$)$_2$]、C[=CHCH$_2$N(CH$_3$)$_2$]、PO($C_{1-4}$ 烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]或键；

A 是 H、OH、SH、NH$_2$、$C_{1-4}$ 烷基、CHF$_2$、CH$_2$F、CF$_3$、CN、CH$_2$OH、CH$_2$O($C_{1-4}$ 烷基)、CH$_2$O($C_{1-4}$ 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、CH$_2$CF$_3$、CF$_2$CF$_3$、CH$_2$OR'CH$_2$C(O)CH=CH$_2$ 或 C(O)CH=CH$_2$；

Z 是 H、CN、NO$_2$、NHC(O)CH$_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、CF$_3$、NO$_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、CF$_3$、NO$_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、C(O)CH$_2$NH$_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、C(O)NH$_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、CH$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO($C_{1-4}$ 烷基)、

$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

45. 权利要求 44 的化合物，其中 A 是 $CH_3$。

46. 权利要求 44 的化合物，其中 $X_4$ 是 O。

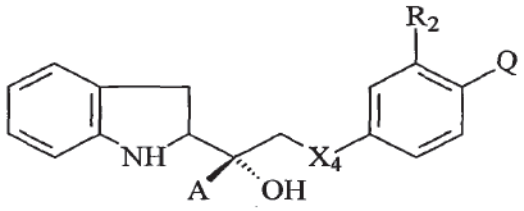
47. 权利要求 44 的化合物，其中 Q 是 CN。

48. 权利要求 44 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

49. 权利要求 44 的化合物，其中 Z 是 CN，Q 是 CN 且 Y 是 $CF_3$。

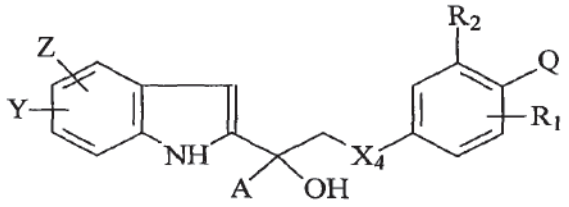
50. 权利要求 44 的化合物，其中 A 是 $CH_3$，$X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$ 和 $R_2$ 是 H，并且 Y 是 $CF_3$。

51. 权利要求 44 的化合物，其由以下结构表示：




。

52. 权利要求 42 的化合物，其中所述化合物由式 XXI 的结构表示：



XXI 。

53. 权利要求 52 的化合物，其中 A 是 $CH_3$。

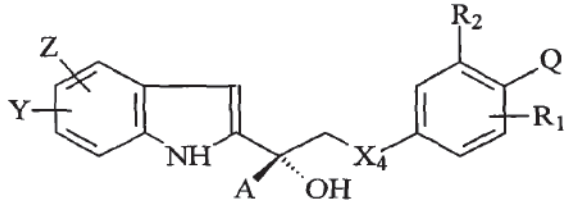
54. 权利要求 52 的化合物，其中 $X_4$ 是 O。

55. 权利要求 52 的化合物，其中 Q 是 CN。

56. 权利要求 52 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

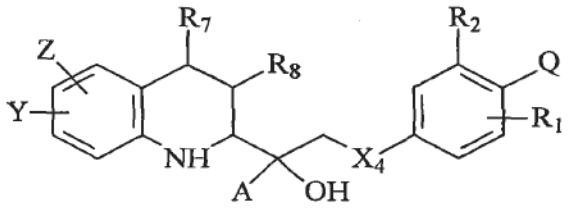
57. 权利要求 52 的化合物，其中 A 是 $CH_3$，$X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$ 和 $R_2$ 是 H，并且 Y 是 $CF_3$。

58. 权利要求 52 的化合物，其由以下结构表示：



。

59. 权利要求 42 的化合物，其中所述化合物由式 XXII 的结构表示：



XXII

其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如式 XX 中所述，$R_7$ 是 H 或氧代，

并且 $R_8$ 是 H 或=$CH_2$。

60. 权利要求 58 的化合物，其中 A 是 $CH_3$。

61. 权利要求 58 的化合物，其中 $X_4$ 是 O。

62. 权利要求 58 的化合物，其中 $R_7$ 和 $R_8$ 是 H。

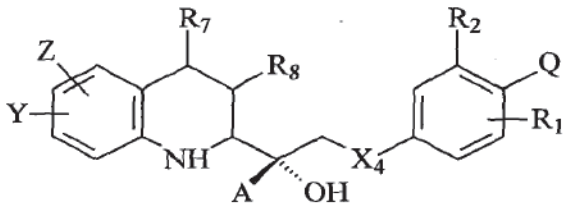
63. 权利要求 58 的化合物，其中 $R_7$ 是=$CH_2$ 且 $R_8$ 是氧代。

64. 权利要求 58 的化合物，其中 Q 是 CN。

65. 权利要求 58 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

66. 权利要求 58 的化合物，其中 A 是 $CH_3$，$X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$ 和 $R_2$ 是 H，并且 Y 是 $CF_3$。

67. 权利要求 58 的化合物，其由以下结构表示：



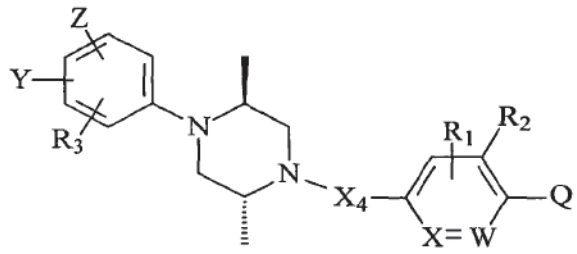

。

68. 权利要求 1 的化合物，其中 P 是式 II，并且 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。

69. 权利要求 68 的化合物，其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是哌嗪、哌嗪-2,6-二酮、哌啶、吡咯烷、环己酮、环己烷、环己烯、环戊酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷

二酮或噁唑烷酮。

70. 权利要求 69 的化合物，其中所述化合物由式 XXIII 的结构表示：



XXIII

X 是 C 或 N；W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

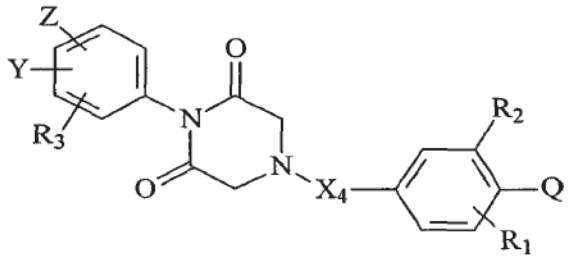
71. 权利要求 70 的化合物，其中 $X_4$ 是 O。

72. 权利要求 70 的化合物，其中 Q 是 CN。

73. 权利要求 70 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

74. 权利要求 70 的化合物，其中 $X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$、$R_2$ 和 $R_3$ 是 H 且 Y 是 $CF_3$。

75. 权利要求68的化合物，其中所述化合物由式XXXIII的结构表示：




XXXIII 。

76. 权利要求 75 的化合物，其中 $X_4$ 是 O。

77. 权利要求 75 的化合物，其中 Q 是 CN。

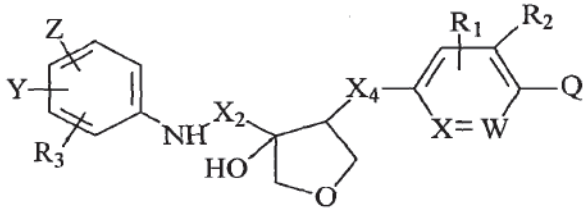
78. 权利要求 75 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

79. 权利要求 75 的化合物，其中 $X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$、$R_2$ 和 $R_3$ 是 H 且 Y 是 $CF_3$。

80. 权利要求 1 的化合物，其中 P 是式 II，$X_3$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。

81. 权利要求 80 的化合物，其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是四氢呋喃、吡咯烷、哌啶、环己酮、环己烷、环己烯、环己烯酮、环戊酮、环戊烯酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷二酮、噁唑烷酮。

82. 权利要求80的化合物，其中所述化合物由式XXXIV的结构表示：



XXXIV

X是C或N；W是C或N；

$X_2$是$C_{1-4}$亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$环)]、CH($C_{1-4}$烷基)、$CH(NH_2)$、CH(OH)、CH($C_{1-4}$卤代烷基)、键；

$X_4$是O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z是H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$烷基、F、Cl、I或Br；

Y是H、$C_{1-4}$烷基、$CF_3$、$NO_2$、CN、F、Cl、I或Br；

Q是H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$烷基)、$C(O)N(C_{1-4}$烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$烷基)、$NHC(O)NH(C_{1-4}$烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$烷基)、$NHSO_2(C_{1-4}$烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$环烷基)]、O-[$CH_2CH_2(C_{4-8}$杂环烷基)]或O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$是H、OH、F、Cl、Br或I；

$R_2$是H、由$R_6$取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或CH=CH-O-对氰基苯基；

$R_3$是H、$C_{1-4}$烷基、卤化物、CN或$NO_2$；

R'是$NH_2$、OH或$CH_3$；并且

$R_6$是CN、$NO_2$、$NHC(O)CH_3$或卤化物。

83. 权利要求82的化合物，其中$X_4$是O。

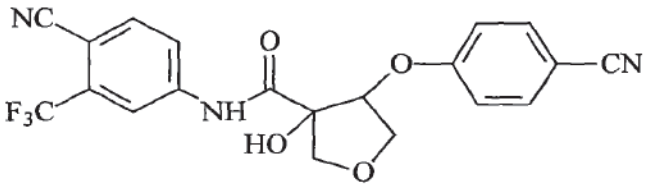
84. 权利要求82的化合物，其中Q是CN。

85. 权利要求 92 的化合物，其中 $X_2$ 是 $CH_2$。

86. 权利要求 82 的化合物，其中 $X_2$ 是 C(O)。

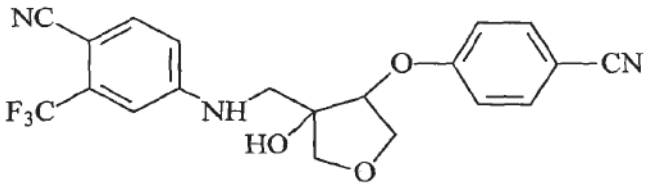
87. 权利要求 82 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

88. 权利要求 82 的化合物，其中所述化合物由式 XXXV 的结构表示：



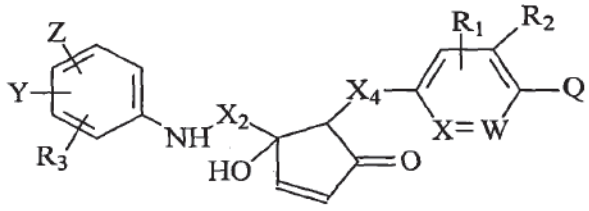
XXXV 。

89. 权利要求 82 的化合物，其中所述化合物由式 XXXVI 的结构表示：



XXXVI 。

90. 权利要求 80 的化合物，其中所述化合物由式 XXXVII 的结构表示：



XXXVII 。

91. 权利要求 90 的化合物，其中 $X_2$ 是 $CH_2$。

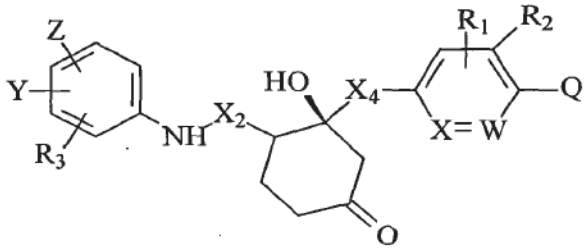
92. 权利要求 90 的化合物，其中 $X_2$ 是 C(O)。

93. 权利要求 90 的化合物，其中 $X_4$ 是 O。

94. 权利要求 90 的化合物，其中 Q 是 CN。

95. 权利要求 90 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

96. 权利要求 80 的化合物，其中所述化合物由式 XXXVIII 的结构表示：




XXXVIII 。

97. 权利要求 96 的化合物，其中 $X_2$ 是 $CH_2$。

98. 权利要求 96 的化合物，其中 $X_2$ 是 C(O)。

99. 权利要求 96 的化合物，其中 $X_4$ 是 O。

100. 权利要求 96 的化合物，其中 Q 是 CN。

101. 权利要求 96 的化合物，其中 Z 是 CN 且 Y 是 $CF_3$。

102. 权利要求 1 的化合物，其中 P 是式 II，并且 $X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

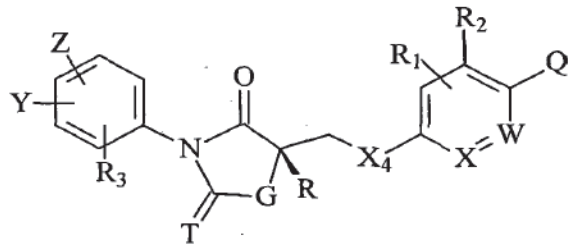
其中

如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；或者

如果 P 是式 II，$R_3$ 是 H，X 和 W 是 C，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成噁唑烷二酮，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

103. 权利要求 102 的化合物，其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、哌啶、吗啉、琥珀酰亚胺、噁唑烷、噁唑烷二酮、噁唑烷酮。

104. 权利要求 102 的化合物，其中所述化合物由式 XXXIX 的结构表示：



XXXIX

其中：

X 是 C 或 N；W 是 C 或 N；

G 是 O、NH、$NC_{1-4}$ 烷基、$NC_{1-4}$ 酰基、S、$CHC_{1-4}$ 烷基、$CHC_{1-4}$ 酰基、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 烷基$)_2$ 或$(CH_2)_n$，其中 n 是 1-3；

T 是 S 或 O；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、

$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

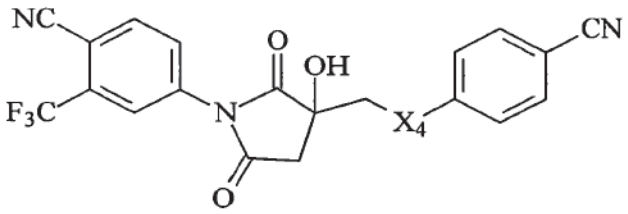
$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

其中如果 $R_3$ 是 H，X 和 W 是 C，G 是 O，T 是 O，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

105. 权利要求 104 的化合物，其中所述化合物由式 XLV 的结构表示：

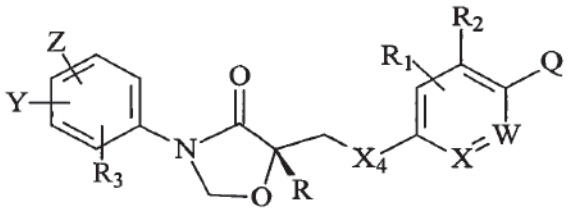


XLV

其中 $X_4$ 如以上关于化合物 XXXIV 所述。

106. 权利要求 105 的化合物，其中 $X_4$ 是 O。

107. 权利要求 102 的化合物，其中所述化合物由式 XLII 的结构表示：



XLII

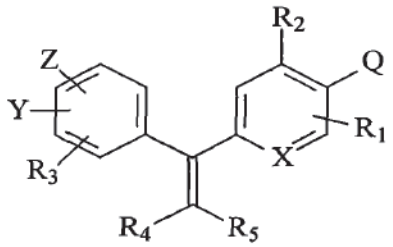
其中：

X、$X_4$、R、$R_1$、$R_2$、$R_3$、Z、Y 和 Q 如以上关于化合物 XXXIV 所述；

其中

如果 X 是 C，$X_4$ 是 O、NH 或 S，$R_1$、$R_2$ 和 $R_3$ 是 H 并且 R 是 H，那么 Q 不是卤素、H 或 CN。

108. 权利要求 1 的化合物，其中所述化合物由式 XLVII 的结构表示：




XLVII

其中

X 是 N 或 CH；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$CH_3$、F、Cl、I 或 Br；

Y 是 H、$CH_3$、$CF_3$、CN、F、Cl、I 或 Br；

Q 是 H、$O-(CH_2)_2CH(CH_3)_2$ 或 $O-(CH_2)_2N(CH_3)_2$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

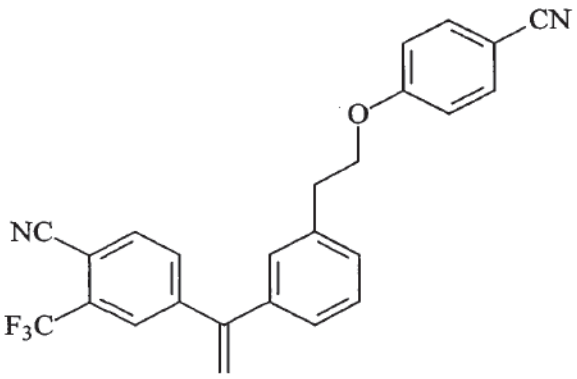
$R_2$ 是由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$CH_3$、卤化物、CN 或 $NO_2$；

$R_4$ 和 $R_5$ 独立地是 H、$CH_3$、卤化物、OH、$C_{1-4}$ 烷基、$C_{1-6}$ 环烷基、卤代-$C_{1-4}$ 烷基、苯基、芳基、杂环或羟基-$C_{1-4}$ 烷基；并且

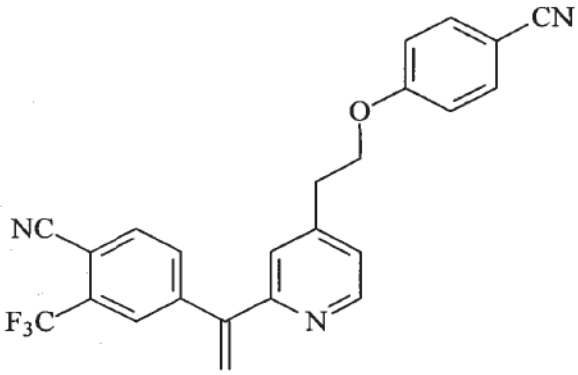
$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

109. 权利要求 108 的化合物，其中所述化合物由式 XLVIII 的结构表示：



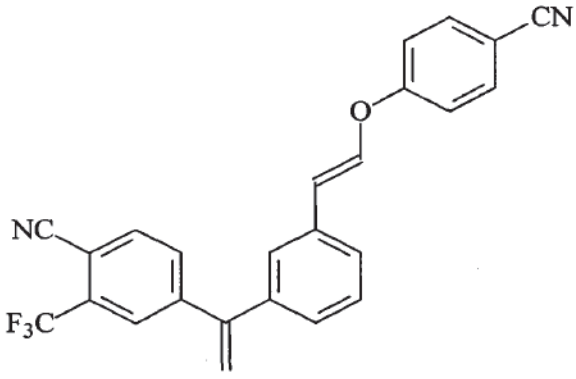
XLVIII 。

110. 权利要求 108 的化合物，其中所述化合物由式 XLIX 的结构表示：



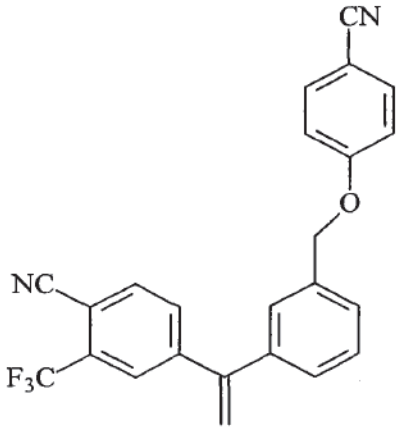
XLIX 。

111. 权利要求 108 的化合物，其中所述化合物由式 L 的结构表示：



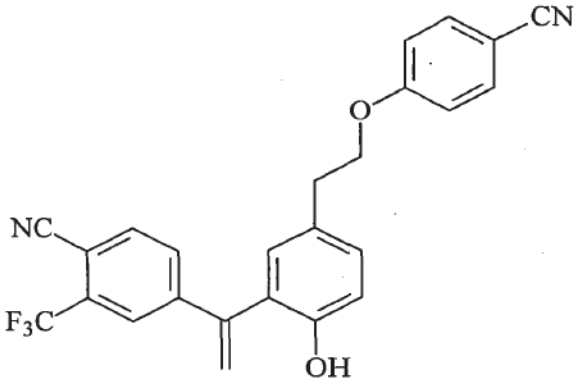
L 。

112. 权利要求 108 的化合物，其中所述化合物由式 LI 的结构表示：



LI 。

113. 权利要求 108 的化合物，其中所述化合物由式 LII 的结构表示：



LII 。

114. 药物组合物，其包含权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、N-氧化物、水合物或它们的任意组合；以及合适的载体或稀释剂。

115. 药物组合物，其包含有效量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、N-氧化物、水合物或它们的任意组合；以及药学上可接受的载体、稀释剂或盐。

116. 在雄性个体中避孕的方法，所述方法包括向所述个体给药有效抑制所述个体中精子产生的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤，由此实现在所述个体中的避孕。

117. 激素治疗方法，所述方法包括使个体的雄激素受体与有效实现改变雄激素依赖性病症的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合接触的步骤。

118. 治疗罹患前列腺癌的个体的方法，所述方法包括向所述个体给药有效治疗所述个体中的前列腺癌的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

119. 延缓罹患前列腺癌的个体的前列腺癌的进展的方法，所述方法包括向所述个体给药有效延缓所述个体中前列腺癌的进展的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

120. 治疗个体的骨相关的病症、或增加个体的骨量、促进个体的骨形成的方法，所述方法包括向所述个体给药有效治疗所述骨相关的病症的量的权利要求 1 的化合物或其异构体、药学上可接受的盐、药品、晶体、水合物、*N*-氧化物或它们的任意组合的步骤。

121. 权利要求 120 的方法，其中所述个体罹患骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱、骨矿物质密度（BMD）丢失或它们的任意组合。

122. 权利要求 120 的方法，其中所述方法增加所述个体的骨强度。

123. 权利要求120的方法，其中所述化合物促进或增强成骨细胞生成。

124. 权利要求120的方法，其中所述化合物抑制破骨细胞增殖。

125. 治疗个体的肌萎缩症、降低其发病率、延缓其进展、减轻其严重性或减轻与其相关的症状的方法，所述方法包括向所述个体给药有效治疗所述个体的所述肌萎缩症的量的权利要求1的化合物或其异构体、药学上可接受的盐、药品、晶体、水合物、*N*-氧化物或它们的任意组合的步骤。

126. 权利要求125的方法，其中所述肌萎缩症归因于病状、疾患、疾病或病症。

127. 权利要求126的方法，其中所述病状、疾患、疾病或病症是神经性的、感染性的、慢性的或遗传性的。

128. 权利要求126的方法，其中所述病状、疾患、疾病或病症是肌营养不良症、肌萎缩、伴X染色体的脊延髓肌萎缩症（SBMA）、恶病质、营养不良、麻风病、糖尿病、肾脏病、慢性阻塞性肺疾病（COPD）、癌症、终末期肾功能衰竭、少肌症、肺气肿、骨软化症、HIV感染、AIDS或心肌病。

129. 权利要求126的方法，其中所述肌萎缩症是年龄相关的肌萎缩症，废用性失调相关的肌萎缩症；或者所述肌萎缩症归因于慢性下腰痛、烧伤、中枢神经系统（CNS）损伤或损害、周围神经损伤或损害、脊髓损伤或损害、化学性损伤或损害、或者酒精中毒。

130. 治疗人类个体的糖尿病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求1的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

131. 治疗患有的人类个体的葡萄糖耐受不良、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

132. 治疗人类个体的高胰岛素血症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

133. 治疗人类个体的胰岛素抵抗、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

134. 治疗与糖尿病相关的疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

135. 治疗人类个体的脂肪肝症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

136. 治疗人类个体的心血管疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

137. 治疗个体的恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

138. 权利要求 137 的方法，其中所述恶病质与所述个体的癌症相关。

139. 治疗个体的类风湿性关节炎、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

140. 治疗个体的慢性肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

141. 治疗个体的终末期肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

142. 治疗个体的脆弱、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

143. 治疗个体的性腺功能减退症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水

合物或它们的任意组合的步骤。

144. 治疗个体的年龄相关的功能减退、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

# 选择性雄激素受体调节剂、它们的类似物和衍生物以及它们的用途

## 交叉引用相关申请

本申请要求2006年7月19日提交的美国临时专利申请60/831880和2006年7月19日提交的美国临时专利申请60/831988的利益；这两件申请以其全部通过引用结合于此。

## 发明领域

本发明提供细胞核激素受体结合化合物、包含它们的组合物以及它们在治疗个体的各种疾病或病症中的使用方法，所述疾病或病症尤其包括前列腺癌、肌萎缩症和与此相关的疾病或病症、和/或骨相关的疾病或病症。

## 发明背景

细胞核激素受体超家族是最大的一类转录因子，涉及广泛的生理过程。该家族的48个成员分为三类，第1类包括雄激素（AR）、雌激素（ER-α和ER-β）、糖皮质激素（GR）、孕酮（PR）和盐皮质激素（MR）的受体。第2类包括类视黄醇、甲状腺和维生素D的受体，而第3类包括其配体有待鉴定的受体（孤儿（orphans））。细胞核激素受体具有功能少有表征的N末端域（NTD）、负责受体与DNA应答元件结合的DNA结合域（DBD）、含有核定位信号的铰链区和结合配体并活化或抑制受体功能的配体结合域（LBD）。而且，存在两个活化功能域，一个位于NTD（AF-1）中，另一个位于LBD（AF-2）中。第I类受体，由于DBD高度的氨基酸序列同源性、LBD的中等同源性以及相似的二级和三级结构特征、和类固醇配体共同的化学特征，经常能与其它第I类受体的配体结合（即交叉反应）。例如，早期对AR和ER的研究表明，类固醇由类固醇A-环与螺旋-3残基接触并且D-环与螺旋-11残基接触而在LBD中的定位，可能对所有类固醇激素受体都是普遍的。

雄激素受体（“AR”）是配体激活的转录调节蛋白，它通过其对内源性雄

激素的活性介导雄性性发育和性功能的诱导。雄激素通常被称为雄性性激素。雄激素是在体内由睾丸和肾上腺皮质产生的类固醇，或者可以在实验室中合成。雄激素类固醇在许多生理过程中起重要作用，包括雄性性征例如肌肉和骨量、前列腺生长、精子发生和雄性毛发模式的产生和维持(Matsumoto，Endocrinol. Met. Clin. N. Am. 23:857-75 (1994))。内源性类固醇雄激素包括睾酮和双氢睾酮（"DHT"）。睾酮是睾丸分泌的主要类固醇，而且是雄性血浆中发现的主要循环雄激素。在许多外周组织中，睾酮由 5α-还原酶转化为DHT。因此，DHT 被认为是大多数雄激素作用的细胞内介质(Zhou 等人, Molec. Endocrinol. 9:208-18 (1995) )。其它类固醇雄激素包括睾酮的酯，例如环戊烷丙酸酯（cypionate）、丙酸酯、苯基丙酸酯（phenylpropionate）、环戊基丙酸酯（cyclopentylpropionate）、异己酸酯（isocarporate）、庚酸酯和癸酸酯，以及其它合成雄激素，例如 7-甲基-去甲睾酮（"MENT"）及其醋酸酯(Sundaram 等人，"7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," Ann. Med., 25:199-205 (1993) ("Sundaram"))。因为 AR 涉及雄性性发育和性功能，所以 AR 可能是实现雄性避孕或其它形式的激素替代疗法的靶标。

人类孕酮受体(PR)存在三种不同的亚型：PR-A、PR-B 和 PR-C(Kastner 等人, EMBO J 9:1603-1614, 1990; Wei 等人, Mol Endo 10:1379-1387, 1996)，其中，PR-A 和 PR-B 是最丰富的。然而，PR-A 亚型对 PR-B 亚型的比率在靶组织中不恒定，这会改变细胞应答，因为各亚型的活性可以变化。

很少有化合物在很多种条件下都显示出部分孕激素活性。RU-486，最普遍使用的抗孕激素，仅在选定的条件下显示出部分激动剂活性。具有部分激动剂活性的抗孕激素化合物对治疗各种孕激素调节的疾病和病症有用，然而，这些很少的已知抗孕激素仅具有有限的部分激动剂活性，本领域仍需要具有广泛的部分激动剂活性的抗孕激素。

世界人口增长和计划生育的社会意识已经促进了大量的避孕研究。避孕无论如何都是一个困难的课题。它伴有文化和社会的烙印，牵涉宗教，最肯定地，它伴有重要的健康关切。当该课题的焦点集中在雄性避孕时，情况只会恶化。尽管存在合适的避孕器械，但是在历史上，社会期望妇女作出避孕的决定并承担后果。虽然对性传播疾病的忧虑使男人更加认识到需要培养安

全和负责的性习惯，但是妇女仍然经常承担避孕选择的主要压力。妇女们有一些选择，从临时的机械装置（例如海绵和子宫帽）到临时的化学方法（例如杀精子药）。妇女们还有一些可支配的更持久的选择，例如物理装置包括宫内节育器和宫颈帽，以及更持久的化学处理，例如避孕丸和皮下埋植剂。然而，至今，男人们仅有的选择包括使用避孕套和输精管切除术。然而，许多男人不喜欢使用避孕套，因为这会减弱性敏感性，干扰性自发，并很有可能因破裂或使用不当而导致怀孕。输精管切除术也不受青睐。如果有更方便的控制生育的方法供男人使用，特别是在性行为之前无需准备活动的长期方法，那么这些方法就能显著地增加男人承担更多的避孕责任的可能性。

雄性类固醇（例如睾酮及其衍生物）的给药在这方面显得特别有潜力，因为这些化合物具有组合的抑制促性腺激素和代替雄激素的性质(Steinberger等人，"Effect of Chronic Administration of Testosterone Enanthate on Sperm Production and Plasma Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels: A Preliminary Evaluation of a Possible Male Contraceptive", Fertility and Sterility 28:1320- 28 (1977) )。长期给药大剂量的睾酮完全停止精子的产生（无精子）或将精子减少至很低的水平（精子减少）。造成不育所需的抑制精子产生的程度还不清楚。然而，世界卫生组织最近的一篇报道显示，每周肌内注射庚酸睾酮造成98%的接受治疗的男性无精子或严重的精子减少（即每毫升小于三百万个精子）和不育(World Health Organization Task Force on Methods And Regulation of Male Fertility，"Contraceptive Efficacy of Testosterone-Induced Azoospermia and Oligospermia in Normal Men," Fertility and Sterility 65:821-29 (1996) )。

已经开发出多种睾酮酯，它们在肌内注射后被吸收得更慢，由此产生更大的雄激素效应。庚酸睾酮是这些酯类中使用最广泛的。尽管庚酸睾酮在确定激素药剂用于雄性避孕的可行性方面有很大价值，但是它具有几个缺点，包括需要每周注射和在肌肉内注射后立即出现睾酮的超生理性最高水平(Wu, "Effects of Testosterone Enanthate in Normal Men: Experience From a Multicenter Contraceptive Efficacy Study," Fertility and Sterility 65:626-36 (1996) ) 。

雄性和雌性的骨矿物质密度（BMD）都随着年龄而降低。骨矿物质含量

（BMC）和 BMD 降低的量与骨强度的减小相关，并容易使患者骨折。

骨质疏松症是全身性骨骼疾病，其特征是骨量少、骨组织退化并导致骨脆弱（bone fragility）和骨折敏感性增加。在美国，该病症影响超过 0.25 亿人口，每年造成超过 130 万例骨折，包括每年 50 万例脊柱骨折、25 万例髋骨折、24 万例腕骨骨折。髋骨折是骨质疏松症最严重的后果，其中 5-20%的患者在一年内死亡，超过 50%的存活者残疾。老人罹患骨质疏松症的风险最大，因此，随着人口老龄化，预计该问题会显著增加。在接下来的 60 年内，全世界的骨折发生率预计将增加三倍，而一项研究估计，2050 年世界上将有 450 万例髋骨折。

妇女罹患骨质疏松症风险比男性更大。在绝经期后的五年中，妇女骨丢失急剧加速。增加风险的其它因素包括吸烟、酒精滥用、久坐的生活习惯和低的钙摄入。然而，骨质疏松症也经常发生于男性身上。十分确定，男性的骨矿物质密度随着年龄而减少。骨矿物质含量和密度的降低与骨强度的减小相关并容易造成骨折。性激素在非生殖组织中的多效性作用的潜在的分子机制仅仅刚开始为人们所认识，但是，清楚的是，生理浓度的雄激素和雌激素在维持整个生命周期中的骨稳态上起重要作用。因此，出现雄激素和雌激素剥夺时，结果是骨重建速度增加，这使吸收和成形的平衡倾向吸收，这导致全身性的骨量丢失。在男性，成熟期性激素的自然减少（雄激素的直接减少以及由雄激素的外周芳构化产生的雌激素的低水平）与骨脆弱相关。在去势的男性中也观察到了这种效应。

肌萎缩是指肌肉量的进行性损失和/或肌肉的进行性衰弱和退化，包括控制运动的骨骼肌或随意肌、控制心脏（心肌病）的心肌和平滑肌。慢性肌萎缩是以肌肉量的进行性损失、肌肉衰弱和退化为特征的慢性病症。

肌萎缩过程中发生的肌肉量损失可以通过分解代谢造成肌肉蛋白的降解来表征。发生蛋白质分解代谢的原因是异常地高速度的蛋白质降解、异常地低速度的蛋白质合成或两者的组合。无论是高程度的蛋白质降解还是低程度的蛋白质合成引起的肌肉蛋白分解代谢都会导致肌肉量的减少和肌萎缩。

肌萎缩与慢性的、神经性的、遗传性的或传染性的病状、疾病、疾患或病症相关。它们包括肌营养不良，例如迪谢内肌营养不良和肌强直性营养不良；肌萎缩，例如小儿麻痹症后肌萎缩（PPMA）；恶病质，例如心源性恶

病质、艾滋病恶病质和癌症恶病质、营养不良、麻风病、糖尿病、肾脏病、慢性阻塞性肺疾病（COPD）、癌症、终末期肾功能衰竭、少肌症、肺气肿、骨软化症、HIV 感染、AIDS 和心肌病。

此外，其它的情况和病症也与肌萎缩有关并能导致肌萎缩。它们包括慢性下腰痛、高龄（advanced age）、中枢神经系统（CNS）损伤、周围神经损伤、脊髓损伤、化学性损伤、中枢神经系统（CNS）损害、周围神经损害、脊髓损害、化学性损害、烧伤、在四肢固定和因疾病或损伤而长期住院时发生的废用性失调（disuse deconditioning）和酒精中毒。

完整的雄激素受体(AR)信号转导途径对于骨骼肌的适当发育十分关键。而且，完整的 AR 信号转导途径增加瘦肌肉量、肌肉强度和肌肉蛋白的合成。

肌萎缩如果不减弱，会造成可怕的健康后果。例如，在肌萎缩过程中发生的变化会导致身体状况变弱，这对个体的健康有害，导致骨折易感性增强和体能状况虚弱。而且，肌萎缩是患恶病质和 AIDS 的病人发病率和死亡率的强烈预兆。

在基础科学和临床水平都急需新的创新方法以开发用于以下的化合物：a) 男性避孕；b) 治疗各种激素相关的病症，例如与衰老男性雄激素减退（ADAM）相关的病症，例如疲劳、抑郁、性欲降低、性功能障碍、勃起功能障碍、性腺功能减退症、骨质疏松症、脱发、贫血、肥胖症、少肌症、骨质减少、骨质疏松症、良性前列腺增生、情绪和认知改变以及前列腺癌；c) 治疗与 ADIF 相关的病症，例如性功能障碍、性欲降低、性腺功能减退症、少肌症、骨质减少、骨质疏松症、认知和情绪改变、抑郁、贫血、脱发、肥胖症、子宫内膜异位症、乳腺癌、子宫癌和卵巢癌；d) 治疗和/或预防慢性肌萎缩或少肌症；e) 减少前列腺癌的发病率、中止前列腺癌或引起前列腺癌消退；f) 口服雄激素替代和/或其它临床治疗和/或诊断领域。

很多种疾病和/或病症都受到性腺功能减退症和分解代谢作用的影响，包括肾病、中枢神经系统损伤、烧伤和慢性伤口。

在美国，肾功能衰竭的发病率上升且十分普遍。登记终末期肾脏疾病（ESRD）医疗保险基金项目的患者数量从 1973 年的约 1 万受益人增加至 1983 年的 86354 人，至 2002 年 12 月 3 日达到 431284 人。单是 2002 年，就有 100359 名患者参加美国 ESRD 项目。慢性肾病（CKD）是 ESRD 的先兆，

它在肾脏不能完全从体内排除废物时发生。CKD 是一种缓慢地进行性疾病，其中，糖尿病、高血压和贫血可能是并发的病症。

CKD 使用表示可用肾功能量的分期系统来诊断（第 1 期=正常肾功能），而且患者在早期通常不会出现症状。CKD 的第 5 期是 ESRD，它是完全或接近完全的肾衰竭，而且通常发生在肾功能低于基线的 10%时。

与 ESRD 相关的伴随症状包括性腺功能减退症、非意愿体重减轻、疲劳等等。

烧伤导致睾酮减少、氮水平下降和骨矿物质密度（BDM）减少，这些在损伤后甚至可能要持续一年之久，并且与伤口愈合不良、感染风险增大、瘦体重减少、复原受阻和延缓烧伤幸存者重返社会有关。因烧伤而引起的分解代谢作用造成显著的非意愿体重减轻，并进一步使问题复杂化。

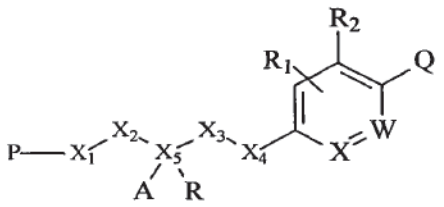
脊髓损伤（SCI）可能会导致改变中枢神经递质的分泌和产生，这继而可能造成下丘脑-垂体-肾上腺轴功能障碍，导致睾酮和其它激素水平的下降。SCI 或其它急性疾病或创伤在特征上包括分解代谢增强伴随合成代谢活动减弱，引发易于损失瘦身体组织的病症。只要分解代谢过程不中断，那么紊乱的营养利用将继续下去。损失瘦体重的影响包括伤口扩展和愈合机制受损。由于营养不良和蛋白缺乏加上固定，脊髓损伤的患者处于高度的患褥疮的风险中。

慢性伤口可以由任意种病症引起，包括糖尿病、循环问题、固定等等。使疾病复杂化（例如在糖尿病中）的是出现神经病，其增加足溃疡的风险。

虽然有许多这些病症的处理和治疗，但是都不理想。由于已显示雄激素受体（AR）信号转导途径增加瘦肌肉量、肌肉强度和肌肉蛋白合成，并且由于性腺功能减退症伴随这些病症，所以靶向 AR 信号转导途径的分子可以用于治疗这些疾病和/或病症。

## 发明内容

在一个实施方案中，本发明提供由式 I 的结构表示的化合物：



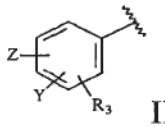
I

其中

X 是 C 或 N；W 是 C 或 N；

$X_1$ 是 N、NH、N($C_{1-4}$ 烷基)、NAc、NCOOH 或键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

P 是 H 或式 II：



II；

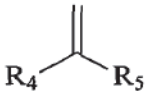
$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、$CH(NH_2)$、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；或者 $X_2$ 和 $R_3$ 与 $X_2$ 所连接的 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_2$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)、键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_3$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；或者 $X_4$ 和 $X_5$ 与 $X_4$ 和 $X_5$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

$X_5$是碳或$X_5$和$X_1$与$X_1$和$X_5$所连接的$X_2$一起形成饱和的或不饱和的、取代的或未取代的5-或6-元环，且A不存在；或者$X_5$和$X_2$形成饱和的或不饱和的、取代的或未取代的5-或6-元环，且A不存在；或者$X_5$和$X_3$形成饱和的或不饱和的、取代的或未取代的5-或6-元环，且A不存在；或$X_5$和$X_4$与$X_5$和$X_4$所连接的$X_3$一起形成饱和的或不饱和的、取代的或未取代的5-或6-元环，且A不存在；

A不存在，或是H、OH、SH、$NH_2$、$C_{1-4}$烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O(C_{1-4}$烷基)、$CH_2O(C_{1-4}$酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'$ $CH_2C(O)CH=CH_2$或$C(O)CH=CH_2$；或者A和R形成式III所表示的双键：



III

Z是H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$烷基、F、Cl、I或Br；

Y是H、$C_{1-4}$烷基、$CH_3$、$NO_2$、CN、F、Cl、I或Br；

Q是H、CN、OH、$NO_2$、卤化物、$CF_3$、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$烷基)、$C(O)N(C_{1-4}$烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$烷基)、$NHC(O)NH(C_{1-4}$烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$烷基)、$NHSO_2(C_{1-4}$烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$环烷基)]、$O-[CH_2CH_2(C_{4-8}$杂环烷基)]或$O-[CH_2CH_2N(CH_3)_2]$；

R是H、OH、$C_{1-4}$烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$烷基)或$O(C_{1-4}$酰基)；

$R_1$是H、OH、$NH_2$、F、Cl、Br或I；

$R_2$是H、由$R_6$取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或CH=CH-O-对氰基苯基；

$R_3$是H、$C_{1-4}$烷基、卤化物、CN、$NO_2$；或$R_3$和$X_2$以及与$R_3$相连的苯环和与$X_2$相连的$X_1$形成饱和的或不饱和的、取代的或未取代的5-或6-元环；

R'是$NH_2$、OH或$CH_3$；

$R_4$和$R_5$独立地是H、$CH_3$、卤化物、OH、$C_{1-4}$烷基、$C_{1-6}$环烷基、卤代($C_{1-4}$烷基)、苯基、芳基、$C_{4-8}$杂环烷基或羟基($C_{1-4}$烷基)；

$R_6$是CN、$NO_2$、$NHC(O)CH_3$或卤化物；

其中

如果P是式II，X是C，$X_1$是NH，$X_2$是C(O)，$X_3$是$CH_2$，R是OH并且A是烷基或卤代烷基，那么$X_4$是$S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$N[CH_2CH_2N(CH_3)_2]$、$P(O)(C_{1-4}$烷基)或$N(O)[CH_2CH_2N(CH_3)_2]$；

或者

如果P是式II，X是C，$X_1$是NH，$X_2$是C(O)，$X_3$是$CH_2$，R是OH或OAlk并且$X_4$是O、S、NH、S、SO、$SO_2$或亚烷基，那么A是CN、$CH_2OH$、$CH_2O(C_{1-4}$烷基)、$CH_2O(C_{1-4}$酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$烷基)、C(O)R'、$CH_2OR'CH_2C(O)CH=CH_2$或$C(O)CH=CH_2$；

或者

如果P是苯基，X是C，$X_1$是NH，$X_2$是C(O)，R是OH并且A是COOH，$X_3$是键，$X_4$是$CH_2$，$R_1$、$R_2$是H，那么Q不是H。

或者

如果P是式II，X是C，$X_3$是$CH_2$，$X_4$是O或NH，$R_1$、$R_2$和$R_3$是H，并且$X_5$和$X_1$形成5元环噁唑烷-2-酮，那么Q不是卤素或H；

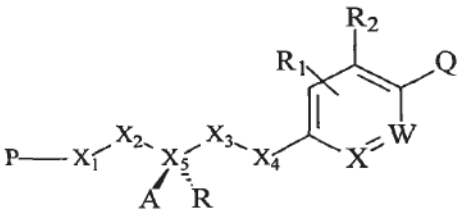
或者

如果P是H，X是C，$X_1$是NH，$X_2$是C(O)，R是OH，A是烷基，$X_3$是键或$CH_2$，并且$X_4$是键或$CH_2$，R1和$R_2$是H，那么Q不是H或卤素

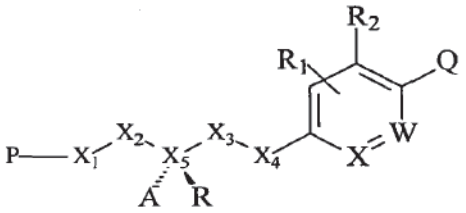
或者

如果P是式II，$R_3$是H，X和W是C，$X_1$和$X_5$与$X_1$和$X_5$所连接的$X_2$一起形成噁唑烷二酮，R是烷基，$X_3$是$CH_2$，并且$X_4$是O、NH、S、$SO_2$或$CH_2$，那么Q不是卤化物。

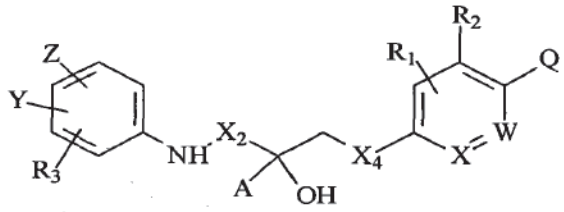
在另一个实施方案中，式I的化合物由以下结构表示：



在另一个实施方案中，式 I 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 IV 的结构表示的化合物：



IV

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CH_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、

$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$;

R 是 H、OH、$C_{1-4}$烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$烷基)或 $O(C_{1-4}$酰基);

$R_1$ 是 H、OH、$NH_2$、F、Cl、Br 或 I;

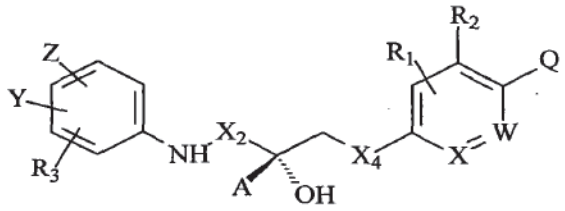
$R_2$ 是 H、由 $R_6$取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基;

$R_3$ 是 H、$C_{1-4}$烷基、卤化物、CN 或 $NO_2$;

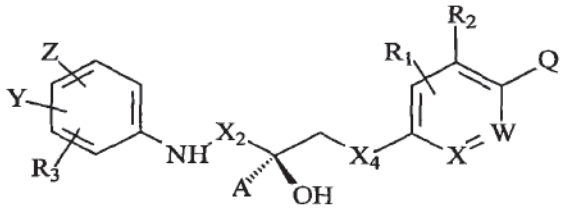
R'是 $NH_2$、OH 或 $CH_3$; 并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

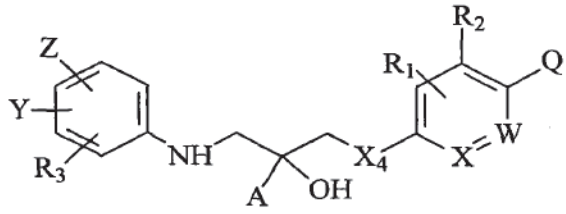
在另一个实施方案中，式 IV 的化合物由以下结构表示:




在另一个实施方案中，式 IV 的化合物由以下结构表示:




在一个实施方案中，本发明提供由式 VI 的结构表示的化合物:




VI

其中

X 是 C 或 N; W 是 C 或 N;

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O(C_{1-4}$ 烷基)、$CH_2O(C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CH_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

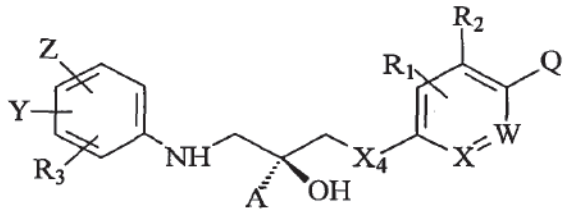
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

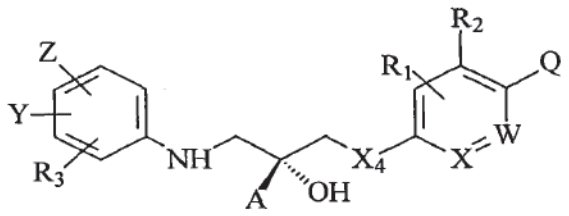
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

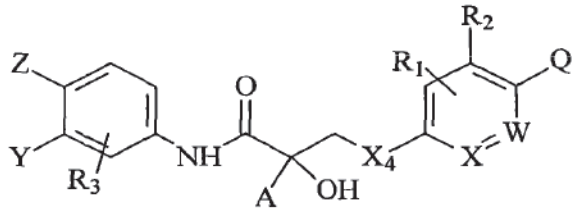
在另一个实施方案中，式 VI 的化合物由以下结构表示：




在一个实施方案中，式 VI 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 XII 的结构表示的化合物：



XII

其中

X 是 C 或 N；W 是 C 或 N；

$X_4$ 是 O、S、SO、S(O)[=CHCH$_2$N(CH$_3$)$_2$]、SO$_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[CH$_2$CH$_2$N(CH$_3$)$_2$]、C[=CHCH$_2$N(CH$_3$)$_2$]、PO($C_{1-4}$ 烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]或键；

A 是 CN、CH$_2$OH、CH$_2$O($C_{1-4}$ 烷基)、CH$_2$O($C_{1-4}$ 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、CH$_2$OR'CH$_2$C(O)CH=CH$_2$ 或 C(O)CH=CH$_2$；

Z 是 H、CN、NO$_2$、NHC(O)CH$_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、CF$_3$、CN、NO$_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO$_2$、CF$_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、C(O)CH$_2$NH$_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、C(O)NH$_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、CH$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO($C_{1-4}$ 烷基)、NHSO$_2$($C_{1-4}$ 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$($C_{4-8}$ 环烷基)]、O-[CH$_2$CH$_2$($C_{4-8}$ 杂环烷基)]或 O-[CH$_2$CH$_2$N(CH$_3$)$_2$]；

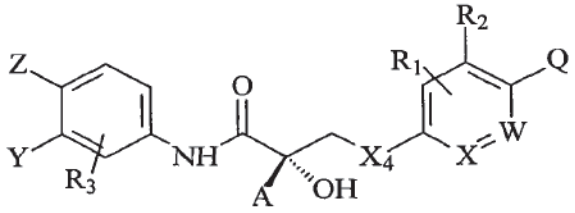
$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、(CH$_2$)$_2$-O-对氰基苯基、CH$_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

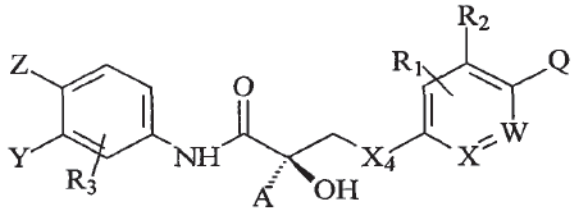
$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 NO$_2$；

R'是 NH$_2$、OH 或 CH$_3$；并且

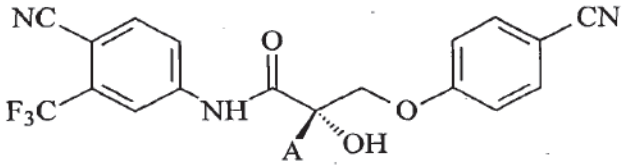
$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：



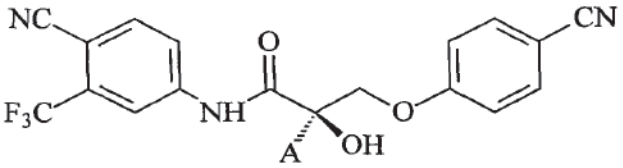
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



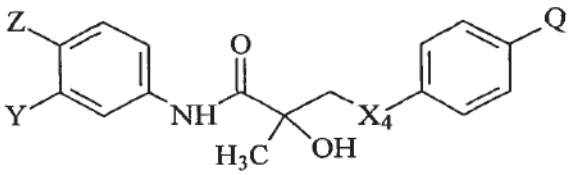
XIII

其中 A 如以上在化合物 XII 中所述。

在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



在一个实施方案中，本发明提供由式 XVII 的结构表示的化合物：



XVII

其中

$X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、

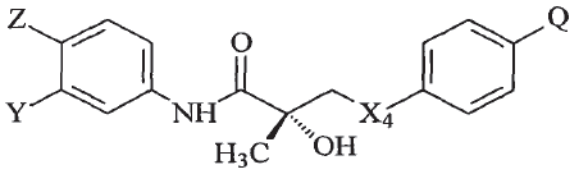
C[=CHCH$_2$N(CH$_3$)$_2$]、PO(C$_{1-4}$ 烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]；

Q 是 H、CN、OH、NO$_2$、CF$_3$、卤化物、C$_{2-6}$ 烯基、C$_{2-6}$ 炔基、C(O)CH$_2$NH$_2$、C(O)NH(C$_{1-4}$ 烷基)、C(O)N(C$_{1-4}$ 烷基)$_2$、C(O)NH$_2$、NH(C$_{1-4}$ 烷基)、NHC(O)NH(C$_{1-4}$ 烷基)、CH$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO(C$_{1-4}$ 烷基)、NHSO$_2$(C$_{1-4}$ 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$(C$_{4-8}$ 环烷基)]、O-[CH$_2$CH$_2$(C$_{4-8}$ 杂环烷基)]或 O-[CH$_2$CH$_2$N(CH$_3$)$_2$]CHF$_2$；

Z 是 H、CN、NO$_2$、NHC(O)CH$_3$、C$_{1-4}$ 烷基、F、Cl、I 或 Br；并且

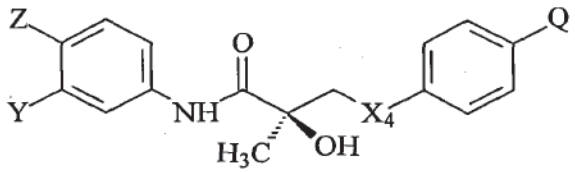
Y 是 H、C$_{1-4}$ 烷基、CF$_3$、CN、NO$_2$、F、Cl、I 或 Br。

在另一个实施方案中，式 XVII 的化合物由以下结构表示：

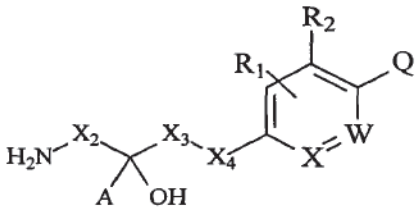


XVII

在另一个实施方案中，式 XVII 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 XIX 的结构表示的化合物：



XIX

其中

X 是 C 或 N；W 是 C 或 N；

X$_2$ 是 C$_{1-4}$ 亚烷基、SO$_2$、C(O)、CH-[CH$_2$-(C$_{4-8}$ 环)]、CH(C$_{1-4}$ 烷基)、CH(NH$_2$)、CH(OH)、CH(C$_{1-4}$ 卤代烷基)、键；

$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)或键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

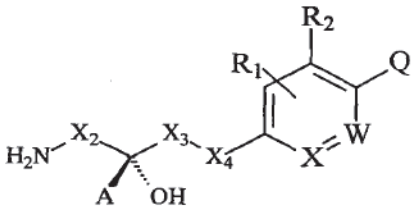
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

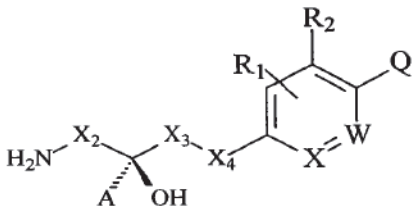
其中

如果 X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$，并且 $X_4$ 是键或 $CH_2$，$R_1$ 和 $R_2$ 是 H，那么 Q 不是 H 或卤素。

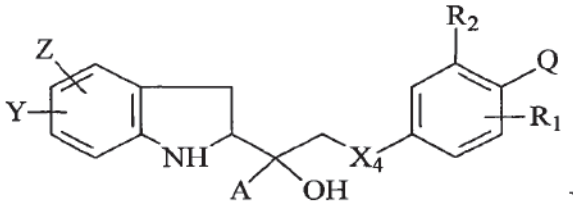
在另一个实施方案中，式 XIX 的化合物由以下结构表示：




在另一个实施方案中，式 XIX 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 XX 的结构表示的化合物：



XX

其中

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

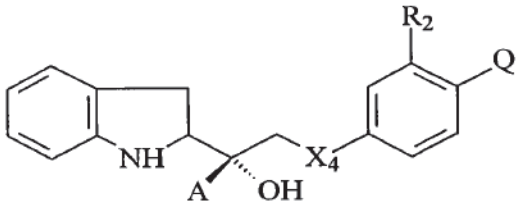
$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

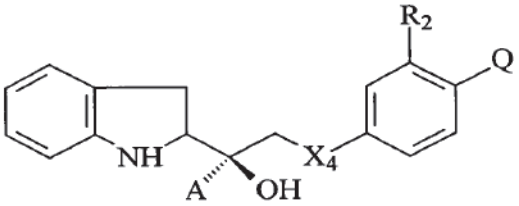
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

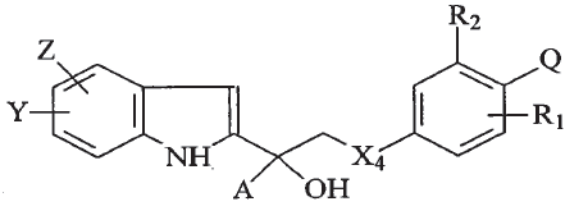
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，



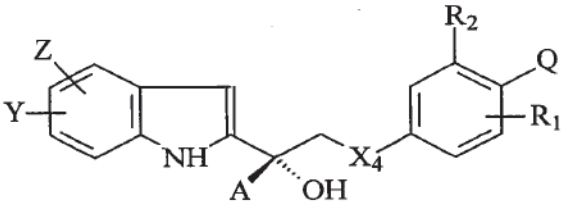
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



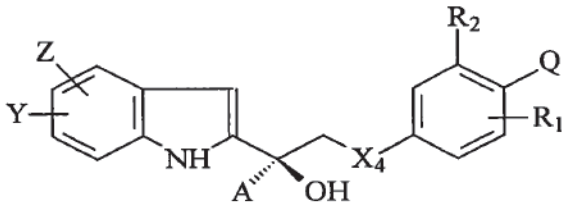
XXI

其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如在化合物 XX 中所述。

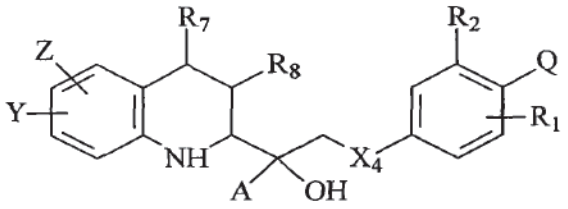
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，



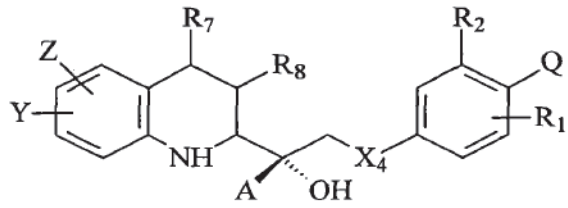
在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



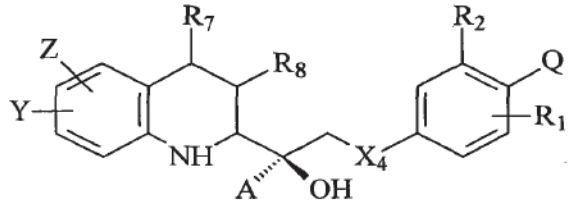
XXII

其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如在化合物 XX 中所述，$R_7$ 是 H 或氧代，$R_8$ 是 H 或=$CH_2$。

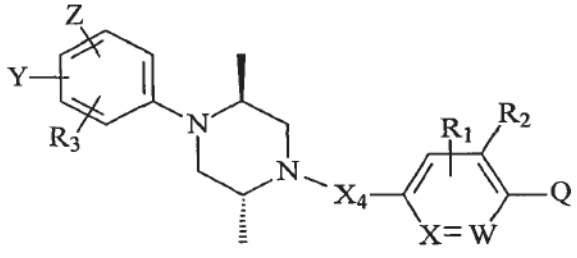
在另一个实施方案中，式 XXII 的化合物由以下结构表示：



或在另一个实施方案中，



在一个实施方案中，本发明提供由式 XXIII 的结构表示的化合物：



XXIII

其中

X 是 C 或 N；W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

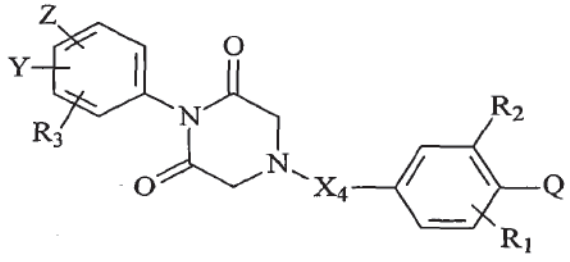
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

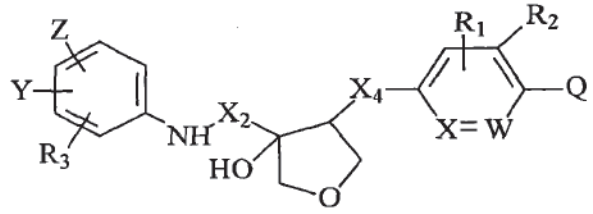
在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



XXXIII

其中 Z、Y、$X_4$、Q、$R_1$、$R_2$ 和 $R_3$ 如在化合物 XXIII 中所述。

在一个实施方案中，本发明提供由式 XXXIV 的结构表示的化合物：



XXXIV

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、$CH-[CH_2-(C_{4-8}$ 环)]、$CH(C_{1-4}$ 烷基)、$CH(NH_2)$、CH(OH)、$CH(C_{1-4}$ 卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、$S(O)[=CHCH_2N(CH_3)_2]$、$SO_2$、NH、NHR'、

NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

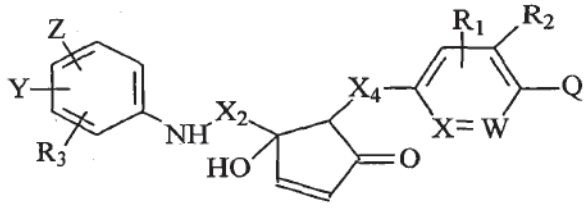
$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

在一个实施方案中，本发明提供由式 XXXVII 的结构表示的化合物：

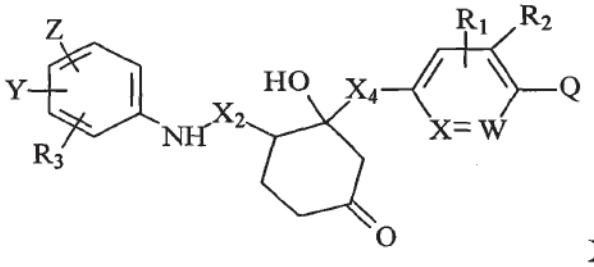


XXXVII

其中

X、$X_2$、$X_4$、Z、Y、Q、R1 和 $R_3$ 如以上在化合物 XXXIV 中所述。

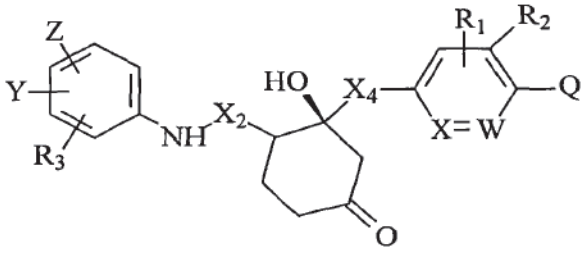
在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：



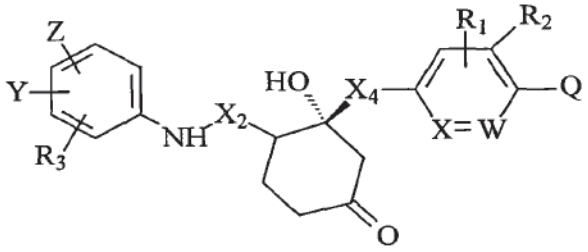
XXXVIII

其中 X、$X_2$、$X_4$、Z、Y、Q、R1 和 $R_3$ 如以上在化合物 XXXIV 中所述。

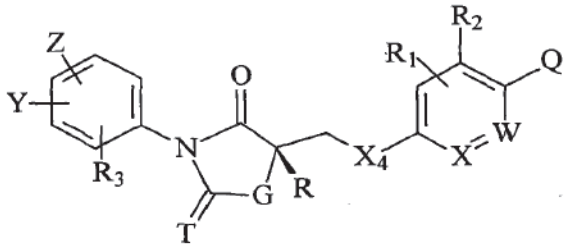
在另一个实施方案中，式 XXXVIII 的化合物由以下结构表示：



或在另一个实施方案中，



在一个实施方案中，本发明提供由式 XXXIX 的结构表示的化合物：



XXXIX

其中：

X 是 C 或 N；W 是 C 或 N；

G 是 O、NH、$NC_{1-4}$ 烷基、$NC_{1-4}$ 酰基、S、$CHC_{1-4}$ 烷基、$CHC_{1-4}$ 酰基、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 烷基$)_2$ 或$(CH_2)_n$，其中 n 是 1-3；

T 是 S 或 O；

$X_4$ 是 O、S、SO、C(O)、S(O)[$=CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[$=CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、

NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$];

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基);

$R_1$ 是 H、OH、F、Cl、Br 或 I;

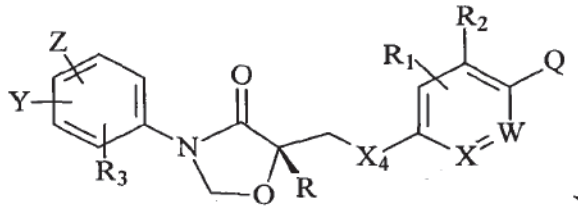
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基;

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$;

R'是 $NH_2$、OH 或 $CH_3$;并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

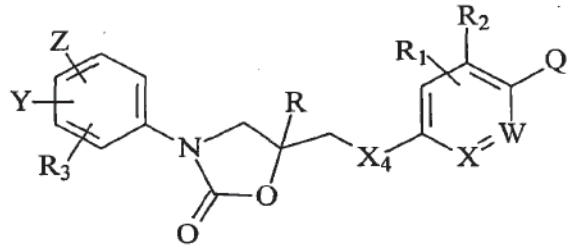
在一个实施方案中,本发明提供式 XLII 的化合物:



XLII

其中 X、$X_4$、Z、Y、Q、R1、$R_2$ 和 $R_3$ 如以上在化合物 XXXIX 中所述。

在一个实施方案中,本发明提供式 XLIV 的化合物:



XLIV

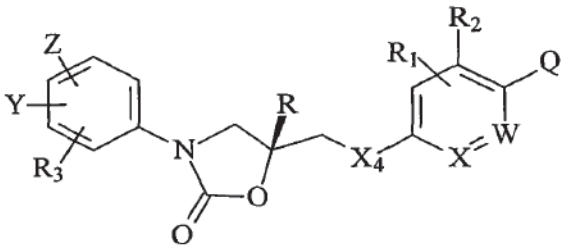
其中:

X、$X_4$、R、$R_1$、$R_2$、$R_3$、Z、Y 和 Q 如以上在化合物 XXXIX 中所述;

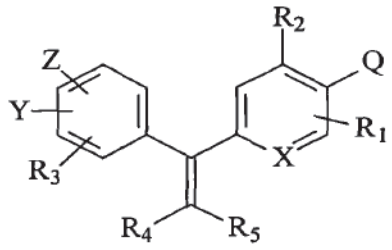
其中

如果 X 是 C,$X_4$ 是 O、NH 或 S,$R_1$、$R_2$ 和 $R_3$ 是 H 并且 R 是 H,那么 Q 不是卤素、H 或 CN。

在另一个实施方案中,式 XLIV 的化合物由以下结构表示:



在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



XLVII

在一个实施方案中，本发明提供组合物，其包含式(I)的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合。

在一个实施方案中，所述化合物是选择性雄激素受体调节剂（SARM）。在一个实施方案中，所述 SARM 是部分激动剂。在一个实施方案中，所述 SARM 是组织选择性激动剂，或在一些实施方案中，是组织选择性拮抗剂。

在一个实施方案中，本发明提供一种在雄性个体中避孕的方法，所述方法包括向所述个体给药有效抑制所述个体中精子产生的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物的步骤，由此实现在所述个体中的避孕。

在一个实施方案中，本发明提供激素治疗方法，所述方法包括使个体的雄激素受体与有效实现改变雄激素依赖性病症的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物接触的步骤。

在一个实施方案中，本发明提供治疗罹患前列腺癌的个体的方法，所述方法包括向所述个体给药有效治疗所述个体中的前列腺癌的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物

或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本发明提供延缓罹患前列腺癌的个体的前列腺癌的进展的方法，所述方法包括向所述个体给药有效延缓所述个体中前列腺癌的进展的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本发明提供治疗个体的骨相关的病症、或增加个体的骨量、促进个体的骨形成的方法，以有效治疗所述骨相关的病症的量给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物。

根据这一方面，在一个实施方案中，所述个体罹患骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱、骨矿物质密度（BMD）丢失或它们的任意组合。在一个实施方案中，所述方法增加所述个体的骨强度。在一个实施方案中，所述化合物促进或加强成骨细胞分化，或者在另一个实施方案中，所述化合物抑制破骨细胞增殖。

在一个实施方案中，本发明提供治疗个体的肌萎缩症、降低其发病率、延缓其进展、减轻其严重性或减轻与其相关症状的方法，所述方法包括向所述个体给药有效治疗所述个体的所述肌萎缩症的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物的步骤。

根据这一方面，在一个实施方案中，所述肌萎缩症归因于病状、疾患、疾病或病症。在一个实施方案中，所述病状、疾患、疾病或病症是神经性的、感染性的、慢性的或遗传性的。在一个实施方案中，所述病状、疾患、疾病或病症是肌肉营养不良症、肌萎缩、伴 X 染色体的（X-linked）脊延髓肌萎缩症（SBMA）、恶病质、营养不良、麻风病、糖尿病、肾脏病、慢性阻塞性肺疾病（COPD）、癌症、终末期肾功能衰竭、少肌症、肺气肿、骨软化症、HIV 感染、AIDS 或心肌病。

在一个实施方案中，所述肌萎缩症是年龄相关的肌萎缩症，废用性失调相关的肌萎缩症；或者所述肌萎缩症归因于慢性下腰痛、烧伤、中枢神经系统（CNS）损伤或损害、周围神经损伤或损害、脊髓损伤、化学性损伤或损害、或者酒精中毒。

在一个实施方案中，本发明提供治疗人类个体的糖尿病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的葡萄糖耐受不良、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的高胰岛素血症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的胰岛素抵抗、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗与糖尿病相关的疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的脂肪肝症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的心血管疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗个体的恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个

体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗个体的眼疾病或病症的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。在一个实施方案中，所述眼疾病或病症包括干燥综合征或干眼病。

在一个实施方案中，本发明提供减少个体脂肪量的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供增加个体瘦体重的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，所述恶病质与所述个体的癌症相关。

在另一个实施方案中，本发明提供治疗个体的类风湿性关节炎、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的慢性肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的终末期肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的脆弱（frailty）、减轻其严

重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的性腺功能减退症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供一种治疗个体的年龄相关的功能减退、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供以下的方法：抑制精子发生；雄性避孕；激素治疗；治疗前列腺癌；延缓前列腺癌的进展；治疗个体的骨相关的疾病或增加个体的骨量和/或促进个体的骨形成；治疗肌萎缩症、降低其发病率、延缓其进程、减轻其严重性或减轻与其相关的症状；治疗糖尿病、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗葡萄糖耐受不良、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗高胰岛素血症、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗胰岛素抵抗、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗与糖尿病相关的疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗脂肪肝症、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗心血管疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗眼疾病或病症；减少脂肪量；或增加个体瘦体重，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤，如本文所述。

**附图简要说明**

在说明书的结论部分特别指出并清楚地要求保护作为本发明的主题。但

是，通过在阅读附图时参照以下的具体描述可以最好地理解关于本发明的组织和操作方法及其目标、特征和优点，其中：

图 1 描绘了各种选择性雄激素受体调节剂类似物的结构（图 1A）和它们的合成路线，例如化合物 XIII（图 1B）、化合物 V（图 1C）、式 XI 的化合物（图 1D）、化合物 XXXV（图 1E）、化合物 XXXVI（图 1F）、化合物 XLVI（图 1G）、化合物 X（图 1H）、化合物 XXIV-XXVIII（图 1I）、化合物 XL（图 1J）、化合物 XLI（图 1K）。

图 2 描绘了制备式 XLIII（oxatidyldione）化合物的合成路线。

图 3 描绘了制备式 XLVIII 化合物的合成路线。

图 4 描绘了制备式 XLIX 化合物的合成路线。

图 5 描绘了制备式 LII 化合物的合成路线。

图 6 描绘了制备式 L 化合物的合成路线。

图 7 描绘了制备式 LI 化合物的合成路线。

图 8 描绘了比卡鲁胺类似物通过野生型雄激素受体的转录激活。在用所示配体处理之前，用 hAR 和雄激素依赖性萤光素酶报告基因构建体短暂转染 CV-1 细胞。报告相对载体处理的对照的增加倍数（n=6）。

图 9 描绘了表 1 中所示的 S-4（图 9A）和睾酮（图 9B）在去势的大鼠中的雄激素活性和合成代谢活性。去势的雄性大鼠在 14 天内接受剂量增加的睾酮（上图）或 S-4（下图）。在处死时测定器官重量，表示为完整对照的百分数。

图 10 描绘了如表 1 中所示的 S-4、S-1、X-2、X-3、X-5 和 X-4（X 分别为 O、O、S、$SO_2$、$CH_2$ 和 NH）的原子以颜色区分的叠加的碳键合氢隐藏的球-棍模型。激动剂 S-4 和 X-2 以及 S-1 显示出以前未对芳基丙酰胺假定过的六元环状 NH-X 氢键构型。

图 11 描绘 DHT、羟基氟他胺（HF）、比卡鲁胺（bical）和 S-4 通过野生型或突变型雄激素受体的转录激活。用野生型或突变型 AR 和雄激素依赖性报告基因构建体的表达载体短暂转染 CV-1 细胞。报告每一种药物（100 nM）AR-介导的诱导，表示为相对萤光素酶单位除以 β-半乳糖苷酶活性（标准化对照）。

图 12 描绘了雄激素受体配体结合域（AR LBD）的晶体结构。图 12A 显

示与*R*-比卡鲁胺结合的突变型AR LBD(W741L)的总体结构的主视图。图12B显示省略了*R*-比卡鲁胺的Fo-Fc模拟退火省略图中的W741L-*R*-比卡鲁胺和*R*-比卡鲁胺的电子密度图。

图13描绘野生型DHT、T877A-HF和W741L-R-比卡鲁胺的立体重叠，显示类固醇结合平面的概观（图13A）和类固醇结合平面的侧视图（图13B）。

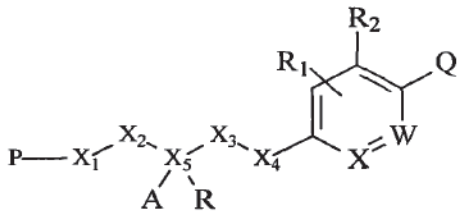
图14描绘了与*R*-比卡鲁胺结合的突变型W741L雄激素受体配体结合域。图14A显示与*R*-比卡鲁胺结合的AR LBD(W741L)的总体结构的侧视图。AF2区（螺旋3、4和12）以绿色突出显示。保守的电荷-发夹（charge-clamp）残基是H3中的K720和H12中的E897。图14B显示与DHT结合的野生型AR LBD的AF2区的结构细节。W741侧链显示在充满原子的空间中。

应理解，为了说明的简单清楚，所述图中所示的元件不一定是按比例绘制的。例如，为了清楚，一些元件的尺寸可能相对于其它元件放大。而且，在认为合适的地方，在所述图中可能重复参考数字以指示相应或类似的元件。

**发明详述**

在以下的具体说明中，叙述了大量的具体细节以提供透彻地理解本发明。然而，本领域的技术人员会理解，没有这些具体细节也可以实施本发明。在其它一些情况下，对众所周知的方法、过程和组分不作详细描述以便不致使本发明变得含混不清。

在一个实施方案中，本发明提供由式I的结构表示的化合物：




I

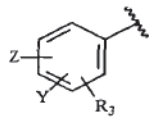
其中

X是C或N；W是C或N；

$X_1$是N、NH、N($C_{1-4}$烷基)、NAc、NCOOH或键；或者$X_1$和$X_3$与$X_1$和$X_3$所连接的$X_2$和$X_5$一起形成饱和的或不饱和的、取代的或未取代的

5-或 6-元环；或者 $X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

P 是 H 或式 II：




II；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；或者 $X_2$ 和 $R_3$ 与 $X_2$ 所连接的 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_2$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

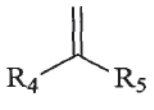
$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)、键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_3$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；或者 $X_4$ 和 $X_5$ 以及与 $X_4$ 和 $X_5$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

$X_5$ 是碳或者 $X_5$ 和 $X_1$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_2$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_3$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_4$ 与 $X_5$ 和 $X_4$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

A 不存在，或是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、

$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'$ $CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；或者 A 和 R 形成式 III 所表示的双键：



III

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、卤化物、$CF_3$、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、$NH_2$、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN、$NO_2$；或者 $R_3$ 和 $X_2$ 与 $R_3$ 所连接的苯环和 $X_2$ 所连接的 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

R'是 $NH_2$、OH 或 $CH_3$；

$R_4$ 和 $R_5$ 独立地是 H、$CH_3$、卤化物、OH、$C_{1-4}$ 烷基、$C_{1-6}$ 环烷基、卤代($C_{1-4}$ 烷基)、苯基、芳基、$C_{4-8}$ 杂环烷基或羟基($C_{1-4}$ 烷基)；

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

其中

如果 P 是式 II，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，$X_3$ 是 $CH_2$，R 是 OH 并且 A 是烷基或卤代烷基，那么 $X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$N[CH_2CH_2N(CH_3)_2]$、$P(O)(C_{1-4}$ 烷基)或 $N(O)[CH_2CH_2N(CH_3)_2]$；

或者

如果 P 是式 II，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，$X_3$ 是 $CH_2$，R 是 OH 或 OAlk 并且 $X_4$ 是 O、S、NH、S、SO、$SO_2$ 或烯基，那么 A 是 CN、$CH_2OH$、

$CH_2O(C_{1-4}$ 烷基)、$CH_2O(C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$ 烷基)、C(O)R'、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

或者

如果 P 是苯基，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH 且 A 是 COOH，$X_3$ 是键，$X_4$ 是 $CH_2$，$R_1$、$R_2$ 是 H，那么 Q 不是 H；

或者

如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

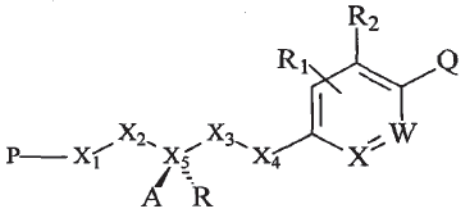
或者

如果 P 是 H，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$，并且 $X_4$ 是键或 $CH_2$，$R_1$ 和 $R_2$ 是 H，那么 Q 不是 H 或卤素；

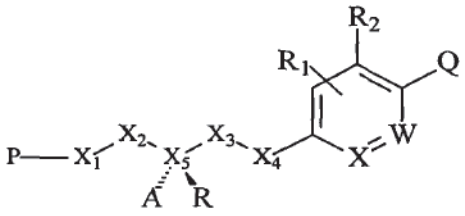
或者

如果 P 是式 II，$R_3$ 是 H，X 和 W 是 C，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 形成噁唑烷二酮，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

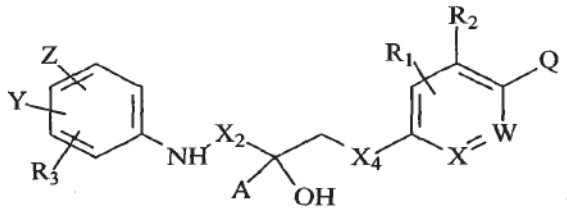
在另一个实施方案中，式 I 的化合物由以下结构表示：



在另一个实施方案中，式 I 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 IV 的结构表示的化合物：



IV

其中

X 是 C 或 N； W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、O($C_{1-4}$ 烷基)或 O($C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、$NH_2$、F、Cl、Br 或 I；

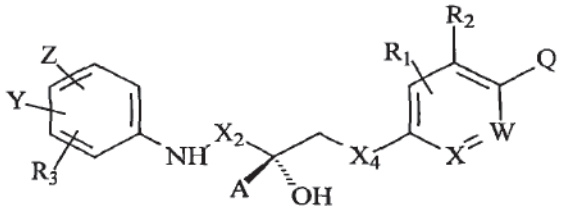
$R_2$ 是 H、$R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

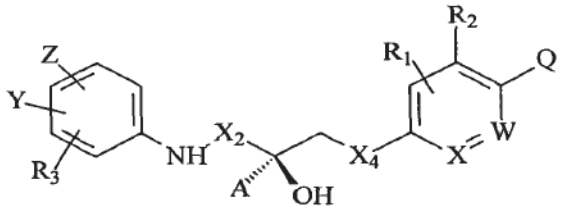
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

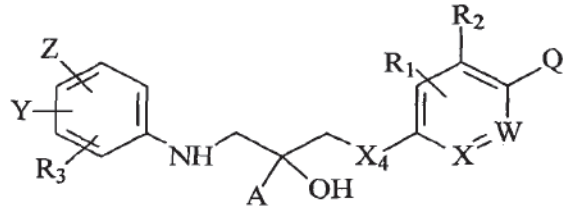
在另一个实施方案中，式 IV 的化合物由以下结构表示：



在另一个实施方案中，式 IV 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 VI 的结构表示的化合物：



VI

其中

X 是 C 或 N； W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O(C_{1-4}$ 烷基)、$CH_2O(C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、

$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

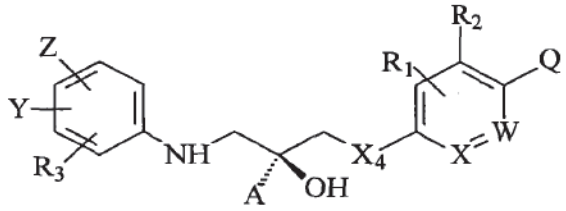
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

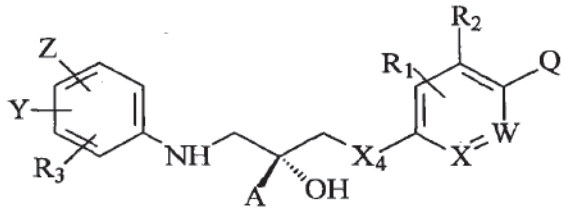
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

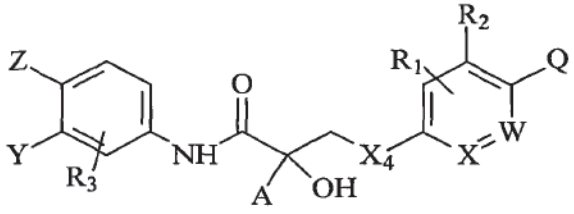
在另一个实施方案中，式 VI 的化合物由以下结构表示：




在一个实施方案中，式 VI 的化合物由以下结构表示：




在一个实施方案中，本发明提供由式 XII 的结构表示的化合物：




XII

其中

X 是 C 或 N；W 是 C 或 N；

$X_4$ 是 O、S、SO、$S(O)[=CHCH_2N(CH_3)_2]$、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基)、

N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 CN、$CH_2OH$、$CH_2O(C_{1-4}$烷基)、$CH_2O(C_{1-4}$酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$烷基)、C(O)R'、$CH_2OR'CH_2C(O)CH=CH_2$或$C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$烷基)、$C(O)N(C_{1-4}$烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$烷基)、$NHC(O)NH(C_{1-4}$烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$烷基)、$NHSO_2(C_{1-4}$烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$环烷基)]、$O-[CH_2CH_2(C_{4-8}$杂环烷基)]或$O-[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

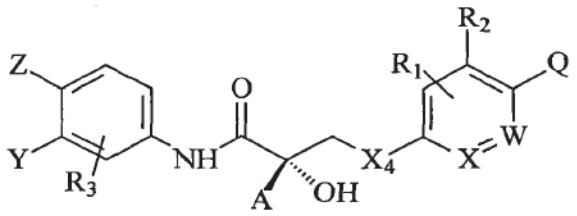
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$烷基、卤化物、CN 或 $NO_2$；

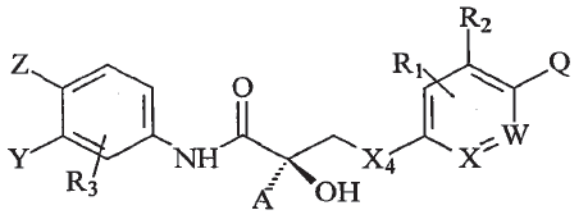
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

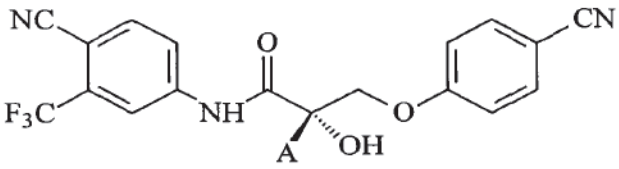
在另一个实施方案中，式 XII 的化合物由以下结构表示：




在另一个实施方案中，式 XII 的化合物由以下结构表示：



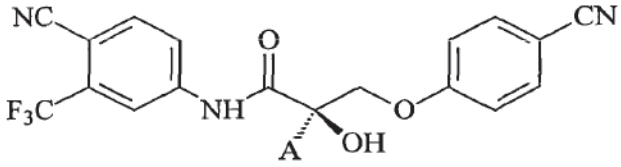

在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



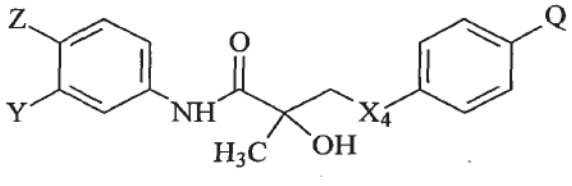
XIII

其中 A 如以上在化合物 XII 中所述。

在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



在一个实施方案中，本发明提供由式 XVII 的结构表示的化合物：



XVII

其中

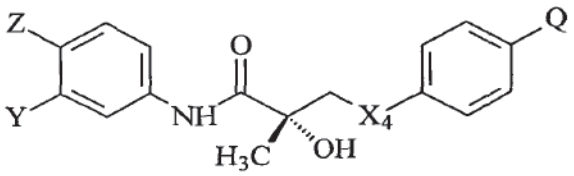
$X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；并且

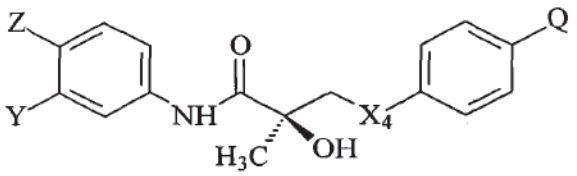
Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br。

在另一个实施方案中，式 XVII 的化合物由以下结构表示：

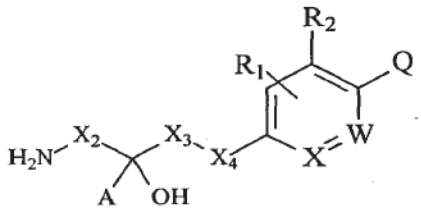


XVII

在另一个实施方案中，式 XVII 的化合物如以下结构表示：



在一个实施方案中，本发明提供由式 XIX 的结构表示的化合物：



XIX

其中

X 是 C 或 N； W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)或键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O\text{-}[CH_2CH_2CH(CH_3)_2]$、$O\text{-}[CH_2CH_2(C_{4-8}$ 环烷基)]、$O\text{-}[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O\text{-}[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

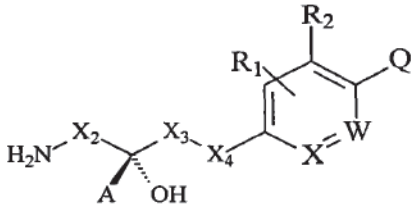
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

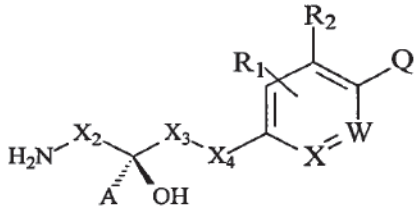
其中

如果 X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$，并且 $X_4$ 是键或 $CH_2$，R1 和 $R_2$ 是 H，那么 Q 不是 H 或卤素。

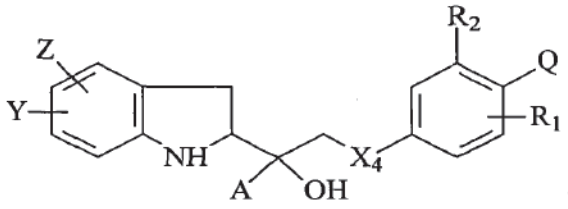
在另一个实施方案中，式 XIX 的化合物由以下结构表示：




在另一个实施方案中，式 XIX 的化合物由以下结构表示：




在一个实施方案中，本发明提供由式 XX 的结构表示的化合物：



XX

其中

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

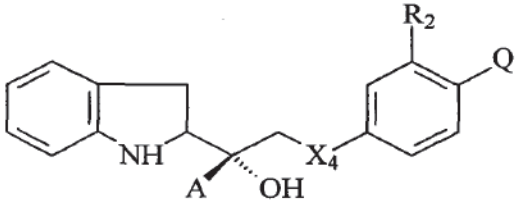
$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

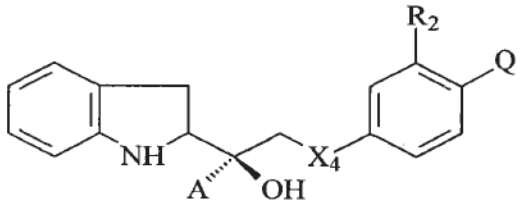
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

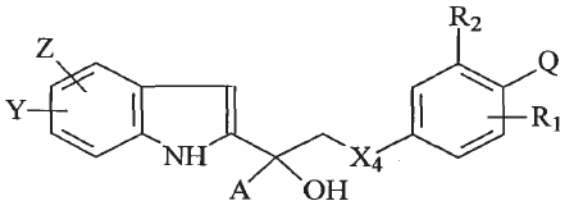
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，



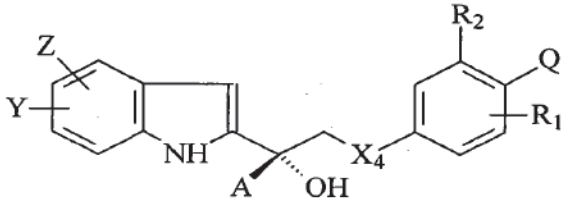
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



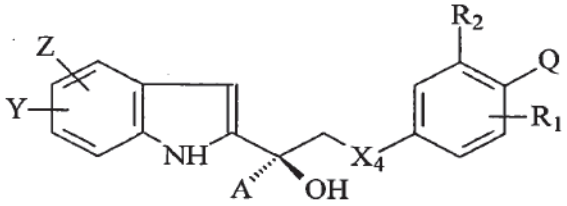
XXI

其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如在化合物 XX 中所述。

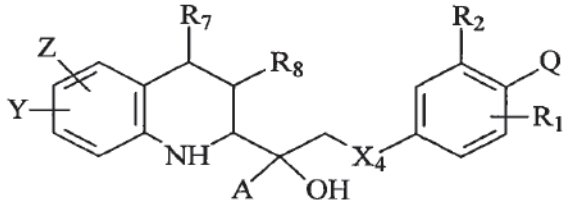
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，



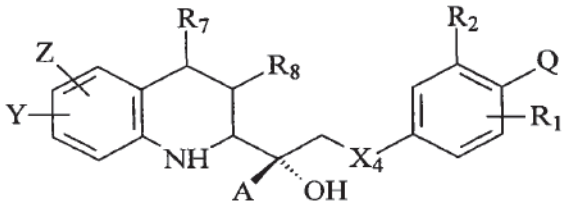
在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



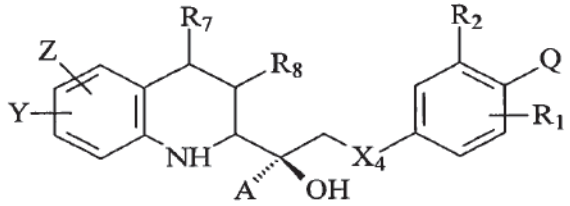
XXII

其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如在化合物 XX 中所述，$R_7$ 是 H 或氧代，$R_8$ 是 H 或=$CH_2$。

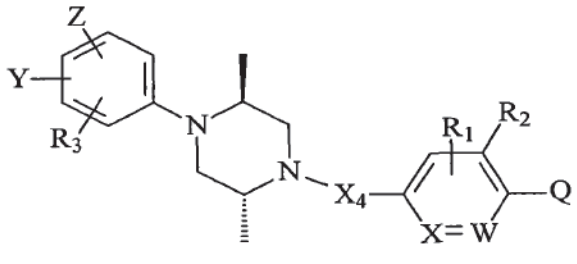
在另一个实施方案中，式 XXII 的化合物由以下结构表示：



或在另一个实施方案中，



在一个实施方案中，本发明提供由式 XXIII 的结构表示的化合物：



XXIII

其中

X 是 C 或 N；W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基

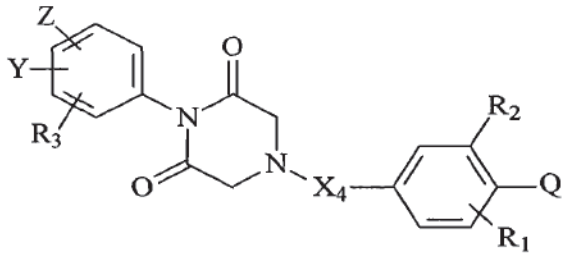
或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

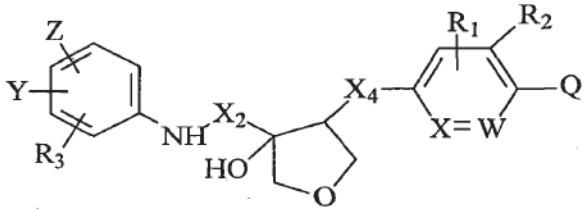
在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



XXXIII

其中 Z、Y、$X_4$、Q、R1 和 $R_3$ 如在化合物 XXIII 中所述。

在一个实施方案中，本发明提供由式 XXXIV 的结构表示的化合物：



XXXIV

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、$CH(NH_2)$、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、

O-[$CH_2CH_2$($C_{4-8}$杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

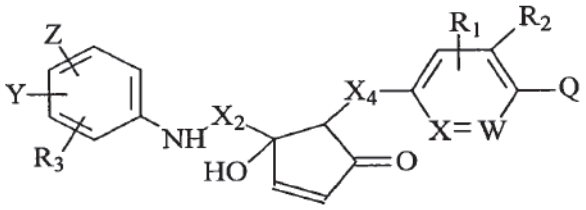
$R_1$是 H、OH、F、Cl、Br 或 I；

$R_2$是 H、由 $R_6$取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$是 H、$C_{1-4}$烷基、卤化物、CN 或 $NO_2$；

$R_6$是 CN、$NO_2$、$NHC(O)CH_3$或卤化物。

在一个实施方案中，本发明提供由式 XXXVII 的结构表示的化合物：

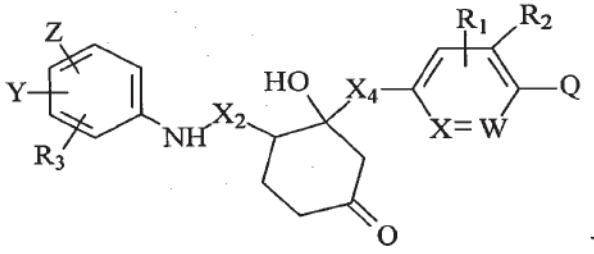


XXXVII

其中

X、$X_2$、$X_4$、Z、Y、Q、$R_1$和 $R_3$如以上在化合物 XXXIV 中所述。

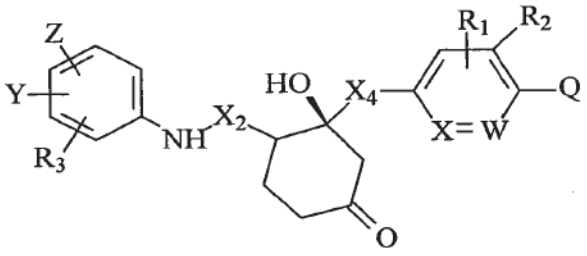
在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：



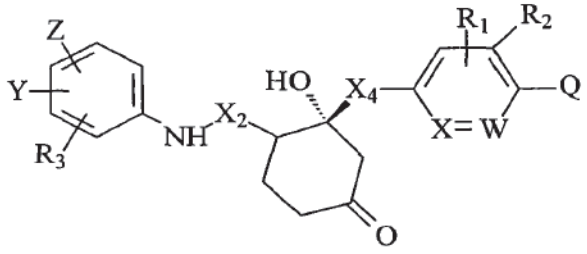
XXXVIII

其中 X、$X_2$、$X_4$、Z、Y、Q、R1 和 $R_3$如以上在化合物 XXXIV 中所述。

在另一个实施方案中，式 XXXVIII 的化合物由以下结构表示：



或在另一个实施方案中，



在另一个实施方案中，化合物 XXXVIII 的 $X_4$ 是 O。在另一个实施方案中，化合物 XXXVIII 的 $X_2$ 是 C(O)。在另一个实施方案中，化合物 XXXVIII 的 $X_2$ 是 $CH_2$。在另一个实施方案中，化合物 XXXVIII 的 Q 是 CN。在另一个实施方案中，化合物 XXXVIII 的 Z 是 CN，并且 Y 是 $CF_3$。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或未饱和的、取代的或未取代的 5-或 6-元环；

其中

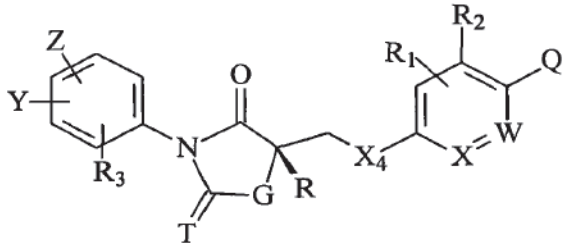
如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

或者

如果 P 是式 II，$R_3$ 是 H，X 和 W 是 C，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成噁唑烷二酮，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

在另一个实施方案中，所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、哌啶、吗啉、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中，本发明提供由式 XXXIX 的结构表示的化合物：



XXXIX

其中：

X 是 C 或 N；W 是 C 或 N；

G 是 O、NH、$NC_{1-4}$ 烷基、$NC_{1-4}$ 酰基、S、$CHC_{1-4}$ 烷基、$CHC_{1-4}$ 酰基、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 烷基$)_2$ 或$(CH_2)_n$，其中 n 是 1-3；

T 是 S 或 O；

$X_4$ 是 O、S、SO、C(O)、S(O)[$=CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[$=CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

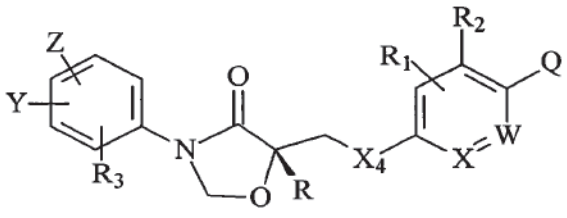
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

其中

如果 $R_3$ 是 H，X 和 W 是 C，G 是 O，T 是 O，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

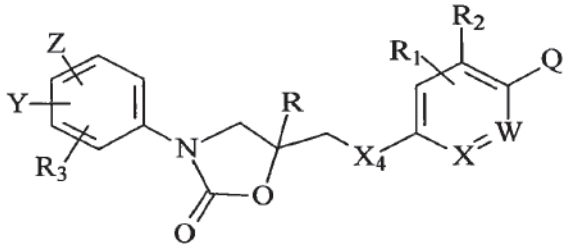
在一个实施方案中，本发明提供式 XLII 的化合物：




XLII

其中 X、$X_4$、Z、Y、Q、R1、$R_2$ 和 $R_3$ 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供式 XLIV 的化合物：



XLIV

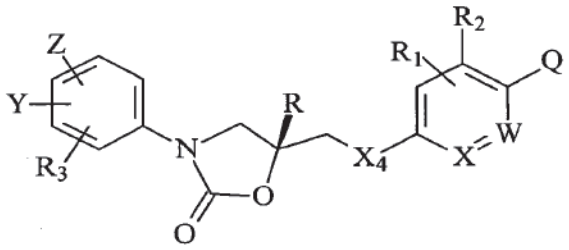
其中：

X、$X_4$、R、$R_1$、$R_2$、$R_3$、Z、Y 和 Q 如以上在化合物 XXXIX 中所述；

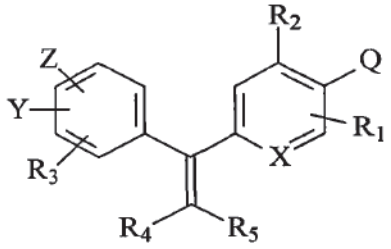
其中

如果 X 是 C，$X_4$ 是 O、NH 或 S，$R_1$、$R_2$ 和 $R_3$ 是 H 并且 R 是 H，那么 Q 不是卤素、H 或 CN。

在另一个实施方案中，式 XLIV 的化合物由以下结构表示：

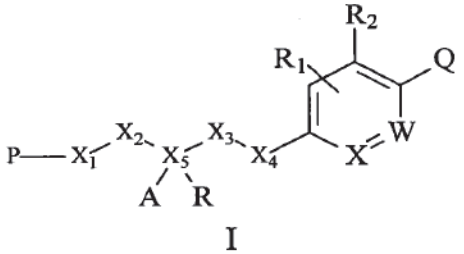


在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



XLVII

在一个实施方案中，本发明提供由式 I 的结构表示的化合物：



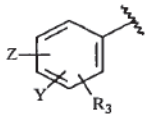
I

其中

X 是 C 或 N；W 是 C 或 N；

$X_1$ 是 N、NH、N($C_{1-4}$ 烷基)、NAc、NCOOH 或键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

P 是 H 或式 II：




II；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；或者 $X_2$ 和 $R_3$ 与 $X_2$ 所连接的 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_2$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

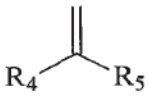
$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)、键；或者 $X_1$ 和 $X_3$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 $X_3$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；或者 $X_4$ 和 $X_5$ 与 $X_4$ 和 $X_5$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_3$ 和 $X_4$ 一起形成双键或形成饱和的或不饱和的、取代的或未取代的 3 至 6 元环；

$X_5$ 是碳或 $X_5$ 和 $X_1$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_2$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 $X_5$ 和 $X_3$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或

$X_5$ 和 $X_4$ 与 $X_5$ 和 $X_4$ 所连接的 $X_3$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

A 不存在，或是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O(C_{1-4}$ 烷基)、$CH_2O(C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'$ $CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；或者 A 和 R 形成式 III 所表示的双键：



III

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、卤化物、$CF_3$、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN、$NO_2$；或 $R_3$ 和 $X_2$ 以及与 $R_3$ 相连的苯环和与 $X_2$ 相连的 $X_1$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

R'是 $NH_2$、OH 或 $CH_3$；

$R_4$ 和 $R_5$ 独立地是 H、$CH_3$、卤化物、OH、$C_{1-4}$ 烷基、$C_{1-6}$ 环烷基、卤代($C_{1-4}$ 烷基)、苯基、芳基、$C_{4-8}$ 杂环烷基或羟基($C_{1-4}$ 烷基)；

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

其中

如果 P 是式 II，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，$X_3$ 是 $CH_2$，R 是 OH 并且 A 是烷基或卤代烷基，那么 $X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$、

$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$N[CH_2CH_2N(CH_3)_2]$、$P(O)(C_{1-4}$烷基)或$N(O)[CH_2CH_2N(CH_3)_2]$；

或者

如果 P 是式 II，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，$X_3$ 是 $CH_2$，R 是 OH 或 OAlk 并且 $X_4$ 是 O、S、NH、S、SO、$SO_2$ 或亚烷基，那么 A 是 CN、$CH_2OH$、$CH_2O(C_{1-4}$烷基)、$CH_2O(C_{1-4}$酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、$C(O)O(C_{1-4}$烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$烷基)、C(O)R'、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

或者

如果 P 是苯基，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH 并且 A 是 COOH，$X_3$ 是键，$X_4$ 是 $CH_2$，$R_1$、$R_2$ 是 H，那么 Q 不是 H。

或者

如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

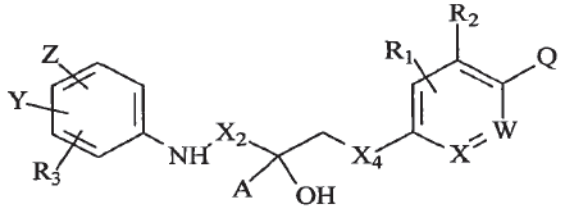
或者

如果 P 是 H，X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O), R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$，并且 $X_4$ 是键或 $CH_2$，R1 和 $R_2$ 是 H，那么 Q 不是 H 或卤素；

或者

如果 P 是式 II，$R_3$ 是 H，X 和 W 是 C，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成噁唑烷二酮，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

在一个实施方案中，本发明提供由式 IV 的结构表示的化合物：




IV

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、CH-[$CH_2$-($C_{4-8}$ 环)]、$CH(C_{1-4}$烷基)、$CH(NH_2)$、CH(OH)、$CH(C_{1-4}$卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、O($C_{1-4}$ 烷基)或 O($C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

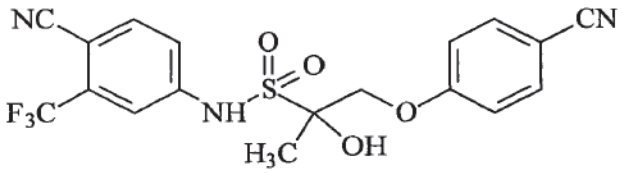
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

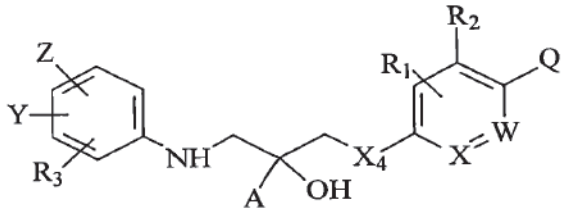
$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

在一个实施方案中，本发明提供由式 V 的结构表示的化合物：



V

在一个实施方案中，本发明提供由式 VI 的结构表示的化合物：



VI

其中

X 是 C 或 N； W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=CHCH$_2$N(CH$_3$)$_2$]、SO$_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[CH$_2$CH$_2$N(CH$_3$)$_2$]、C[=CHCH$_2$N(CH$_3$)$_2$]、PO($C_{1-4}$ 烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]或键；

A 是 H、OH、SH、NH$_2$、$C_{1-4}$ 烷基、CHF$_2$、CH$_2$F、CF$_3$、CN、CH$_2$OH、CH$_2$O($C_{1-4}$ 烷基)、CH$_2$O($C_{1-4}$ 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、CH$_2$CF$_3$、CF$_2$CF$_3$、CH$_2$OR'CH$_2$C(O)CH=CH$_2$ 或 C(O)CH=CH$_2$；

Z 是 H、CN、NO$_2$、NHC(O)CH$_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、CF$_3$、CN、NO$_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO$_2$、CF$_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、C(O)CH$_2$NH$_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、C(O)NH$_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、CH$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO($C_{1-4}$ 烷基)、NHSO$_2$($C_{1-4}$ 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$($C_{4-8}$ 环烷基)]、O-[CH$_2$CH$_2$($C_{4-8}$ 杂环烷基)]或 O-[CH$_2$CH$_2$N(CH$_3$)$_2$]；

R 是 H、OH、$C_{1-4}$ 烷基、CF$_3$、CH$_2$OH、O($C_{1-4}$ 烷基)或 O($C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

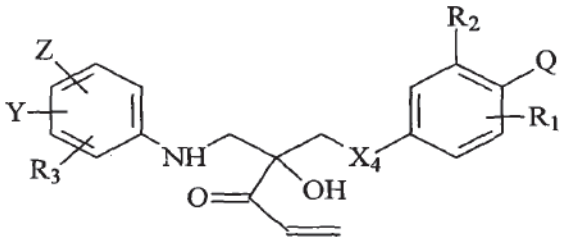
$R_2$ 是 H、由 $R_6$ 取代的苄基、(CH$_2$)$_2$-O-对氰基苯基、CH$_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 NO$_2$；

R'是 NH$_2$、OH 或 CH$_3$； 并且

$R_6$ 是 CN、NO$_2$、NHC(O)CH$_3$ 或卤化物。

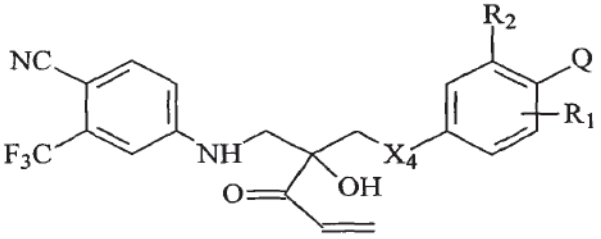
在一个实施方案中，本发明提供由式 VII 的结构表示的化合物：



VII

其中 Z、Y、$R_1$、$R_2$、$R_3$、Q 和 $X_4$ 如以上在化合物 VI 中所述。

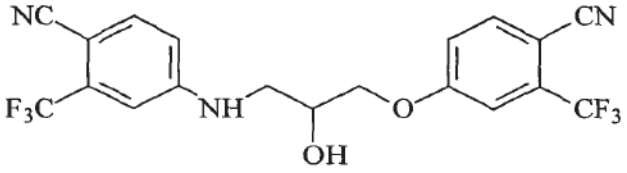
在另一个实施方案中，本发明提供由式 VIII 的结构表示的化合物：



VIII

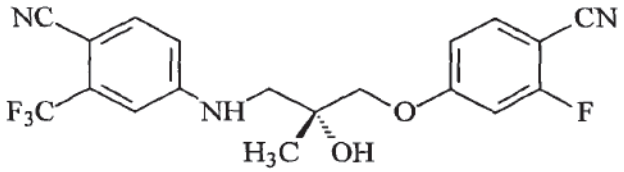
其中 $R_1$、$R_2$、Q 和 $X_4$ 如以上在化合物 VI 中所述。

在一个实施方案中，本发明提供由式 IX 的结构表示的化合物：



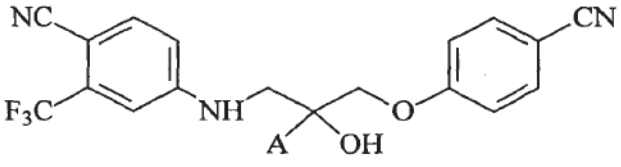
IX **8**

在一个实施方案中，本发明提供由式 X 的结构表示的化合物：



X

在一个实施方案中，本发明提供由式 XI 的结构表示的化合物：



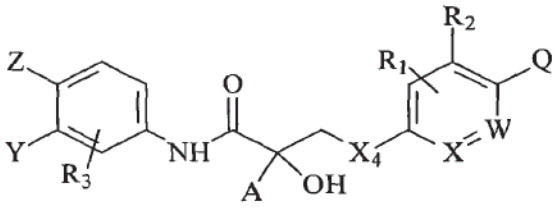
XI

其中 A 如以上在化合物 VI 中所述。

在另一个实施方案中，化合物 XI 的 A 是 $CH_2OH$。在另一个实施方案中，化合物 XI 的 A 是 $CH_2OMe$。在另一个实施方案中，化合物 XI 的 A 是

$CF_3$。在另一个实施方案中，化合物 XI 的 A 是 $CH_3$。在另一个实施方案中，化合物 XI 的 A 是 CN。

在一个实施方案中，本发明提供由式 XII 的结构表示的化合物：



XII

其中

X 是 C 或 N； W 是 C 或 N；

$X_4$ 是 O、S、SO、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、$R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

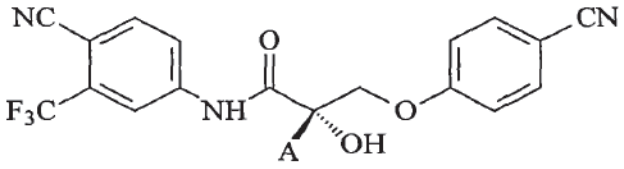
R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

在另一个实施方案中，化合物 XII 的 $X_4$ 是 O。在另一个实施方案中，化合物 XII 的 Q 是 CN，并且 $R_1$ 和 $R_2$ 是 H。在另一个实施方案中，化合物

XII 的 Q 是 CN，Z 是 CN，Y 是 $CF_3$，并且 $R_1$、$R_2$ 和 $R_3$ 是 H。在另一个实施方案中，化合物 XII 的 A 是 $CH_2OH$。在另一个实施方案中，化合物 XII 的 A 是 CN。

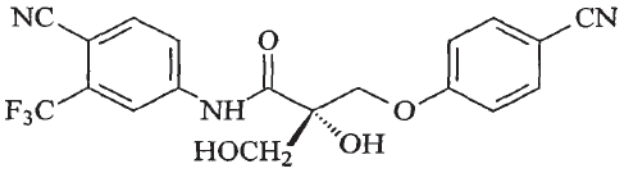
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



XIII

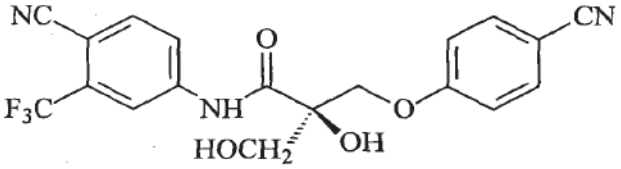
其中 A 如以上在化合物 XII 中所述。

在一个实施方案中，本发明提供由式 XIV 的结构表示的化合物：

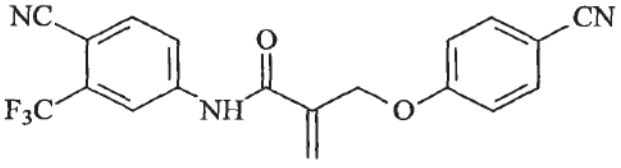


XIV

或在另一个实施方案中，

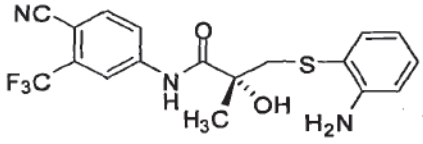


在一个实施方案中，本发明提供由式 XV 的结构表示的化合物：



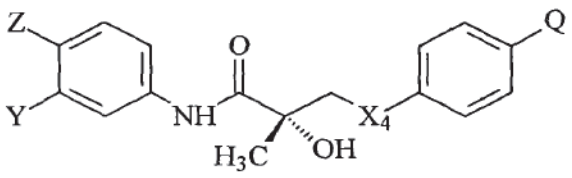
XV

在一个实施方案中，本发明提供由式 XVI 的结构表示的化合物：



XVI

在一个实施方案中，本发明提供由式 XVII 的结构表示的化合物：



XVII

其中

$X_4$ 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$；

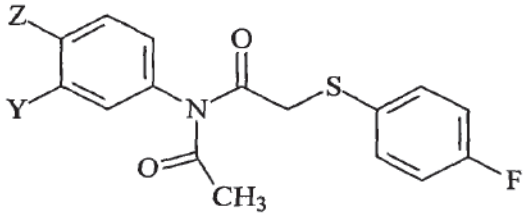
Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；并且

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、CN、$NO_2$、F、Cl、I 或 Br。

在另一个实施方案中，化合物 XVII 的 Q 是 F。在另一个实施方案中，化合物 XVII 的 Q 是 CN。在另一个实施方案中，化合物 XVII 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XVII 的 Q 是 CN，Z 是 CN，并且 Y 是 $CF_3$。

在一个实施方案中，本发明提供由式 XVIII 的结构表示的化合物：



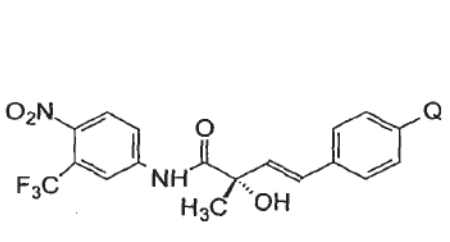
XVIII

在一个实施方案中，本发明提供由式 XIX 的结构表示的化合物：

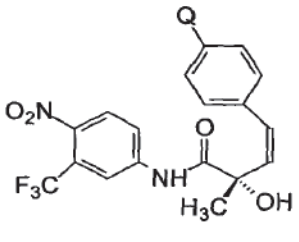
在一个实施方案中，本发明提供式 I 的化合物，其中 $X_3$ 和 $X_4$ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环。在另一个实施方案中，所述 3-6 元环是环丙基、环丁基、环戊基、环己基、环丁烯基、环戊烯基、环己烯基、苯、哌啶、吡咯、四氢呋喃、吡咯烷、琥珀

酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在另一个实施方案中，本发明提供由式 LIII 的结构表示的化合物：

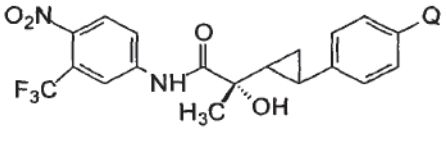


或

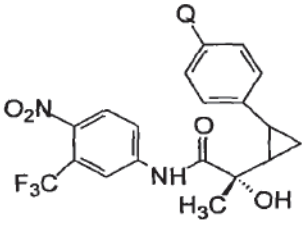


LIII-反式 LIII-顺式

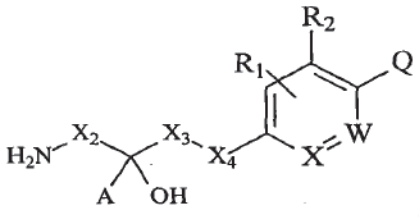
在另一个实施方案中，本发明提供由式 LIV 的结构表示的化合物：



或



LIV LIV



XIX

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_3$ 是 $C_{1-4}$ 亚烷基、NH、N、CH(OH)或键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、

$C(O)O(C_{1-4}$ 烷基)、CONHR'、$C(O)N(R')_2$、$C(O)O(C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；

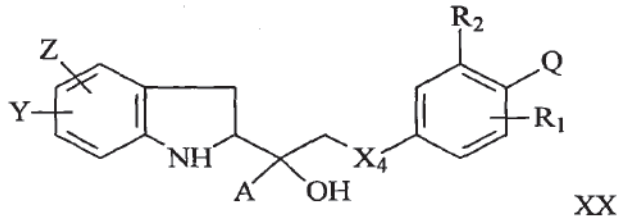
其中

如果 X 是 C，$X_1$ 是 NH，$X_2$ 是 C(O)，R 是 OH，A 是烷基，$X_3$ 是键或 $CH_2$，并且 $X_4$ 是键或 $CH_2$，$R_1$ 和 $R_2$ 是 H，那么 Q 不是 H 或卤素。

在另一个实施方案中，化合物 XIX 的 $X_2$ 是 $CH_2$。在另一个实施方案中，化合物 XIX 的 $X_2$ 是 C(O)。在另一个实施方案中，化合物 XIX 的 $X_3$ 是 CH2。在另一个实施方案中，化合物 XIX 的 $X_4$ 是 O。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，$X_2$ 和 $X_3$ 与 $X_1$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。在另一个实施方案中，所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、吡咯、吗啉、哌啶-4-酮或哌啶。

在一个实施方案中，本发明提供由式 XX 的结构表示的化合物：




XX

I

其中

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

A 是 H、OH、SH、$NH_2$、$C_{1-4}$ 烷基、$CHF_2$、$CH_2F$、$CF_3$、CN、$CH_2OH$、$CH_2O$($C_{1-4}$ 烷基)、$CH_2O$($C_{1-4}$ 酰基)、$CH_2CN$、$CH_2N_3$、$CH_2NCS$、CHO、C(O)O($C_{1-4}$ 烷基)、CONHR'、C(O)N(R')$_2$、C(O)O($C_{1-4}$ 烷基)、C(O)R'、$CH_2CF_3$、$CF_2CF_3$、$CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、C(O)NH($C_{1-4}$ 烷基)、C(O)N($C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、NH($C_{1-4}$ 烷基)、NHC(O)NH($C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、NHCO($C_{1-4}$ 烷基)、$NHSO_2$($C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2$($C_{4-8}$ 环烷基)]、O-[$CH_2CH_2$($C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

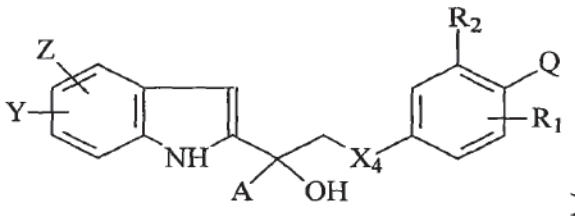
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

在另一个实施方案中，化合物 XX 的 A 是 $CH_3$。在另一个实施方案中，化合物 XX 的 $X_4$ 是 O。在另一个实施方案中，化合物 XX 的 Q 是 CN。在另一个实施方案中，化合物 XX 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XX 的 Q 是 CN，Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XX 的 A 是 $CH_3$，$X_4$ 是 O，Q 是 CN，Z 是 CN，$R_1$ 和 $R_2$ 是 H，并且 Y 是 $CF_3$。

在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：

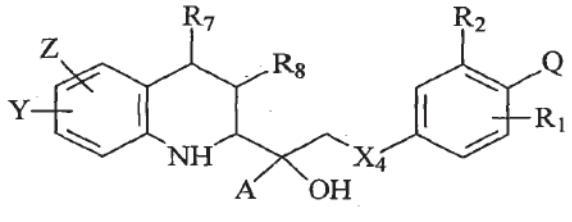


XXI

其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如在化合物 XXI 中所述。

在另一个实施方案中，化合物 XXI 的 A 是 $CH_3$。在另一个实施方案中，化合物 XXI 的 $X_4$ 是 O。在另一个实施方案中，化合物 XXI 的 Q 是 CN。在另一个实施方案中，化合物 XXI 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XXI 的 Q 是 CN，Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XXI 的 A 是 $CH_3$，$X_4$ 是 O，Q 是 CN，Z 是 CN，$R_1$ 和 $R_2$ 是 H，并且 Y 是 $CF_3$。

在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



XXII

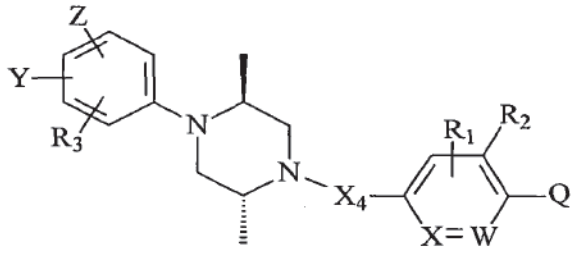
其中 A、Z、Y、$X_4$、Q、$R_1$ 和 $R_2$ 如在化合物 XX 中所述，$R_7$ 是 H 或氧代，$R_8$ 是 H 或=$CH_2$。

在另一个实施方案中，化合物 XXII 的 A 是 $CH_3$。在另一个实施方案中，化合物 XXII 的 $X_4$ 是 O。在另一个实施方案中，化合物 XXI 的 $R_7$ 和 $R_8$ 是 H。在另一个实施方案中，化合物 XXII 的 $R_7$ 是=$CH_2$，并且 $R_8$ 是氧代。在另一个实施方案中，化合物 XXII 的 Q 是 CN。在另一个实施方案中，化合物 XXII 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XXII 的 A 是 $CH_3$，$X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$ 和 $R_2$ 是 H，并且 Y 是 $CF_3$。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，$X_3$ 和 $X_1$ 与 $X_1$ 和 $X_3$ 所连接的 $X_2$ 和 $X_5$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。在另一个实施方案中，所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是哌嗪、哌嗪-2,6-二酮、哌啶、吡咯烷、环己酮、

环己烷、环己烯、环戊酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中，本发明提供由式 XXIII 的结构表示的化合物：




XXIII

其中

X 是 C 或 N； W 是 C 或 N；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$ 烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$ 烯基、$C_{2-6}$ 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、O-[$CH_2CH_2CH(CH_3)_2$]、O-[$CH_2CH_2(C_{4-8}$ 环烷基)]、O-[$CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O-[$CH_2CH_2N(CH_3)_2$]；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

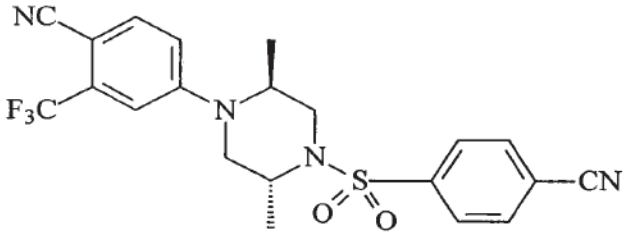
$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

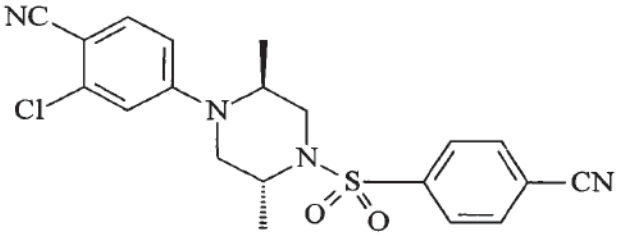
在另一个实施方案中，化合物 XXIII 的 $X_4$ 是 O。在另一个实施方案中，化合物 XXIII 的 Q 是 CN。在另一个实施方案中，化合物 XXIII 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XXIII 的 $X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 Y 是 $CF_3$。

在另一个实施方案中，本发明提供由式 XXIV 的结构表示的化合物：



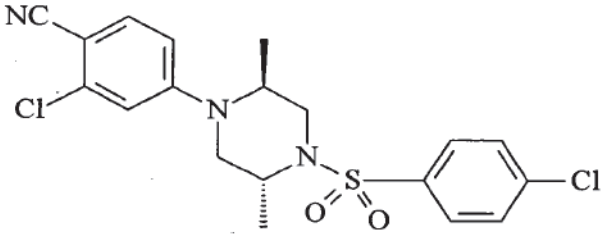
XXIV

在另一个实施方案中，本发明提供由式 XXV 的结构表示的化合物：



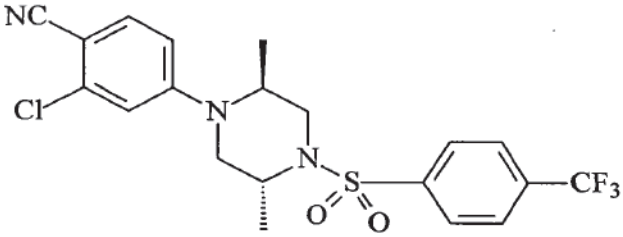
XXV

在另一个实施方案中，本发明提供由式 XXVI 的结构表示的化合物：



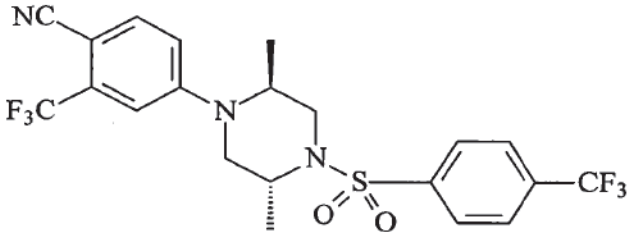
XXVI

在另一个实施方案中，本发明提供由式 XXVII 的结构表示的化合物：



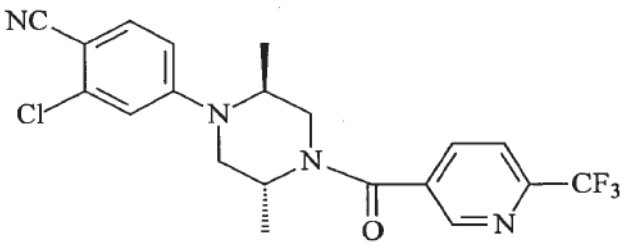
XXVII

在另一个实施方案中，本发明提供由式 XXVIII 的结构表示的化合物：



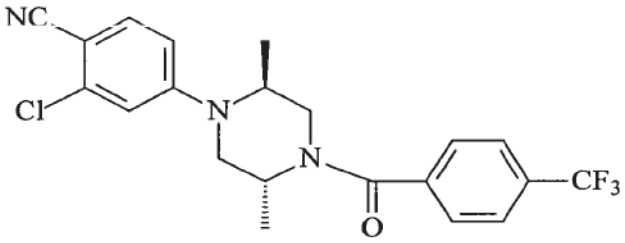
XXVIII

在另一个实施方案中，本发明提供由式 XXIX 的结构表示的化合物：



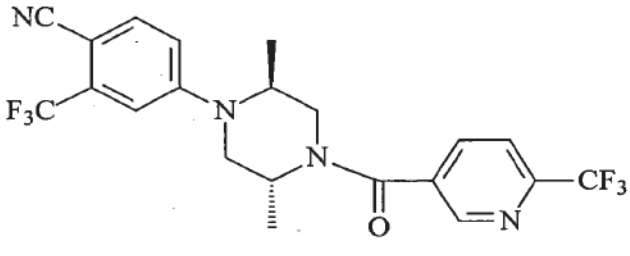
XXIX

在另一个实施方案中，本发明提供由式 XXX 的结构表示的化合物：



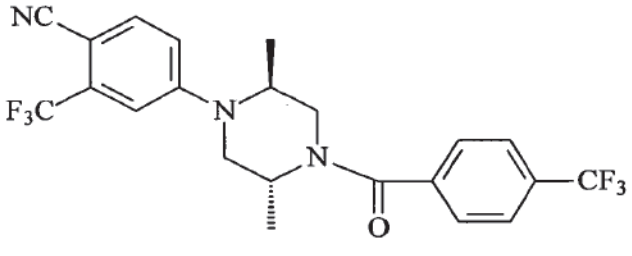
XXX

在另一个实施方案中，本发明提供由式 XXXI 的结构表示的化合物：



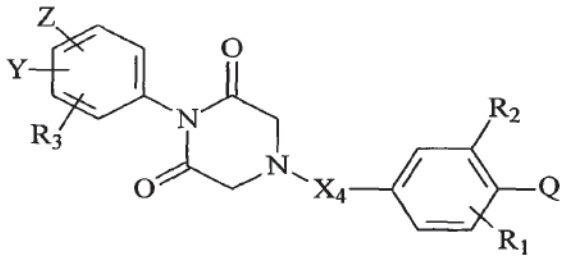
XXXI

在另一个实施方案中，本发明提供由式 XXXII 的结构表示的化合物：



XXXII

在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



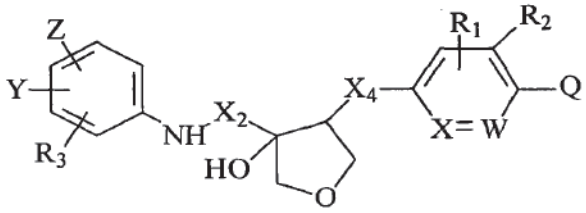
XXXIII

其中 Z、Y、$X_4$、Q、$R_1$、$R_2$ 和 $R_3$ 如在化合物 XXIII 中所述。

在另一个实施方案中，化合物 XXXIII 的 $X_4$ 是 O。在另一个实施方案中，化合物 XXXIII 的 Q 是 CN。在另一个实施方案中，化合物 XXXIII 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XXXIII 的 $X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 Y 是 $CF_3$。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，$X_3$ 和 $X_5$ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。在另一个实施方案中，所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是四氢呋喃、吡咯烷、哌啶、环己酮、环己烷、环己烯、环己烯酮、环戊酮、环戊烯酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中，本发明提供由式 XXXIV 的结构表示的化合物：



XXXIV

XXXIV

其中

X 是 C 或 N；W 是 C 或 N；

$X_2$ 是 $C_{1-4}$ 亚烷基、$SO_2$、C(O)、CH-[$CH_2$-($C_{4-8}$ 环)]、CH($C_{1-4}$ 烷基)、CH($NH_2$)、CH(OH)、CH($C_{1-4}$ 卤代烷基)、键；

$X_4$ 是 O、S、SO、C(O)、S(O)[=$CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[=$CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$NO_2$、$CF_3$、卤化物、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

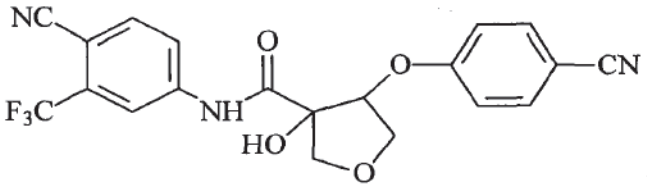
$R_3$ 是 H、$C_{1-4}$烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；和

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

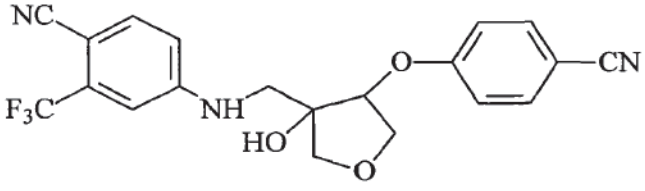
在另一个实施方案中，化合物 XXXIV 的 $X_4$ 是 O。在另一个实施方案中，化合物 XXXIV 的 Q 是 CN。在另一个实施方案中，化合物 XXXIV 的 $X_2$ 是 $CH_2$。在另一个实施方案中，化合物 XXXIV 的 $X_2$ 是 C(O)。在另一个实施方案中，化合物 XXXIV 的 Z 是 CN，并且 Y 是 $CF_3$。在另一个实施方案中，化合物 XXXIV 的 $X_4$ 是 O，Z 是 CN，Q 是 CN，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 Y 是 $CF_3$。

在另一个实施方案中，本发明提供式 XXXV 的化合物：



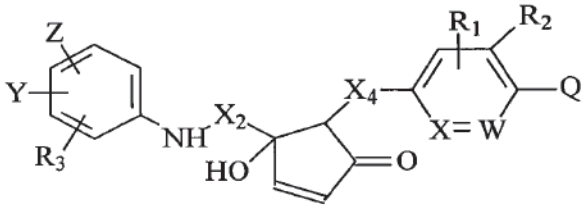

XXXV

在另一个实施方案中，本发明提供式 XXXVI 的化合物：




XXXVI

在一个实施方案中，本发明提供由式 XXXVII 的结构表示的化合物：



XXXVII

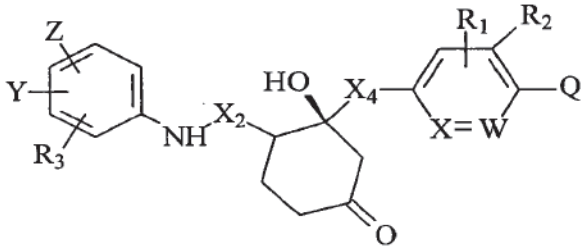
XXXVII

其中

X、$X_2$、$X_4$、Z、Y、Q、$R_1$、$R_2$和$R_3$如以上在化合物 XXXIV 中所述。

在另一个实施方案中，化合物 XXXVII 的$X_4$是 O。在另一个实施方案中，化合物 XXXVII 的$X_2$是 C(O)。在另一个实施方案中，化合物 XXXVII 的$X_2$是$CH_2$。在另一个实施方案中，化合物 XXXVII 的 Q 是 CN。在另一个实施方案中，化合物 XXXVII 的 Z 是 CN，并且 Y 是$CF_3$。

在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：



XXXVIII

其中 X、$X_2$、$X_4$、Z、Y、Q、$R_1$、$R_2$和$R_3$如以上在化合物 XXXIV 中所述。

在另一个实施方案中，化合物 XXXVIII 的$X_4$是 O。在另一个实施方案中，化合物 XXXVIII 的$X_2$是 C(O)。在另一个实施方案中，化合物 XXXVIII 的$X_2$是$CH_2$。在另一个实施方案中，化合物 XXXVIII 的 Q 是 CN。在另一个实施方案中，化合物 XXXVIII 的 Z 是 CN，并且 Y 是$CF_3$。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，$X_1$和$X_5$与$X_1$和$X_5$所连接的$X_2$一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

其中

如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

其中

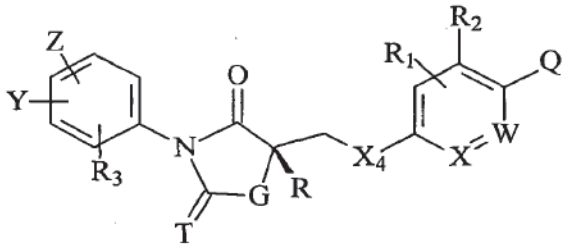
如果 P 是式 II，X 是 C，$X_3$ 是 $CH_2$，$X_4$ 是 O 或 NH，$R_1$、$R_2$ 和 $R_3$ 是 H，并且 $X_5$ 和 $X_1$ 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

或者

如果 P 是式 II，$R_3$ 是 H，X 和 W 是 C，$X_1$ 和 $X_5$ 与 $X_1$ 和 $X_5$ 所连接的 $X_2$ 一起形成噁唑烷二酮，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

在另一个实施方案中，所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、哌啶、吗啉、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中，本发明提供由式 XXXIX 的结构表示的化合物：



XXXIX

其中：

X 是 C 或 N；W 是 C 或 N；

G 是 O、NH、$NC_{1-4}$ 烷基、$NC_{1-4}$ 酰基、S、$CHC_{1-4}$ 烷基、$CHC_{1-4}$ 酰基、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 烷基$)_2$ 或$(CH_2)_n$，其中 n 是 1-3；

T 是 S 或 O；

$X_4$ 是 O、S、SO、C(O)、S(O)[$=CHCH_2N(CH_3)_2$]、$SO_2$、NH、NHR'、NO、$C_{1-4}$ 亚烷基、C(OH)[$CH_2CH_2N(CH_3)_2$]、C[$=CHCH_2N(CH_3)_2$]、PO($C_{1-4}$ 烷基)、N[$CH_2CH_2N(CH_3)_2$]、NO[$CH_2CH_2N(CH_3)_2$]或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$ 烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$烷基)、$C(O)N(C_{1-4}$烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$烷基)、$NHC(O)NH(C_{1-4}$烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$烷基)、$NHSO_2(C_{1-4}$烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$环烷基)]、$O-[CH_2CH_2(C_{4-8}$杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$烷基)或 $O(C_{1-4}$酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

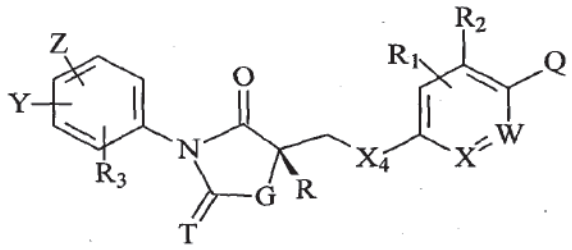
$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$C_{1-4}$烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

在一个实施方案中，本发明提供由式 XXXIX 的结构表示的化合物：



XXXIX

其中：

X 是 C 或 N；W 是 C 或 N；

G 是 O、NH、$NC_{1-4}$烷基、$NC_{1-4}$酰基、S、$CHC_{1-4}$烷基、$CHC_{1-4}$酰基、$C(C_{1-4}$酰基$)_2$、$C(C_{1-4}$烷基$)_2$ 或 $(CH_2)_n$，其中 n 是 1-3；

T 是 S 或 O；

$X_4$ 是 O、S、SO、C(O)、$S(O)[=CHCH_2N(CH_3)_2]$、$SO_2$、NH、NHR'、NO、$C_{1-4}$亚烷基、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$或键；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$C_{1-4}$烷基、F、Cl、I 或 Br；

Y 是 H、$C_{1-4}$烷基、$CF_3$、$NO_2$、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、$CF_3$、$NO_2$、卤化物、$C_{2-6}$烯基、$C_{2-6}$炔基、$C(O)CH_2NH_2$、

$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基)$_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$；

R 是 H、OH、$C_{1-4}$ 烷基、$CF_3$、$CH_2OH$、$O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基)；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

$R_2$ 是 H、由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

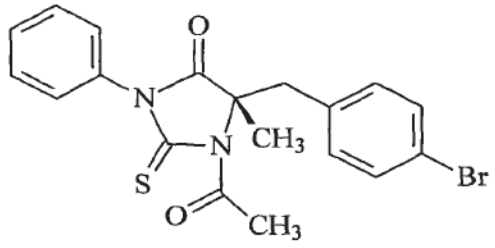
$R_3$ 是 H、$C_{1-4}$ 烷基、卤化物、CN 或 $NO_2$；

R'是 $NH_2$、OH 或 $CH_3$；并且

$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物；其中

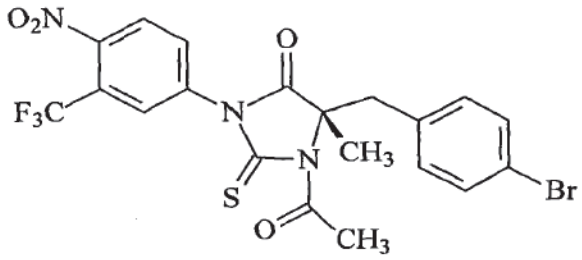
如果 $R_3$ 是 H，X 和 W 是 C，G 是 O，T 是 O，R 是烷基，$X_3$ 是 $CH_2$，并且 $X_4$ 是 O、NH、S、$SO_2$ 或 $CH_2$，那么 Q 不是卤化物。

在一个实施方案中，本发明提供式 XL 的化合物：



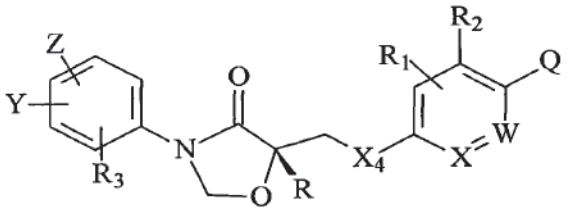
XL

在一个实施方案中，本发明提供式 XLI 的化合物：



XLI

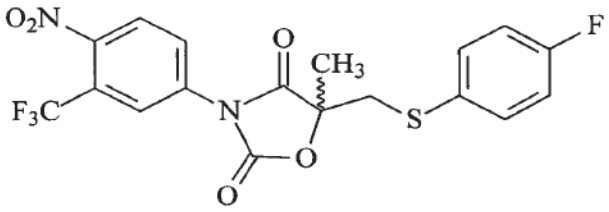
在一个实施方案中，本发明提供式 XLII 的化合物：



XLII

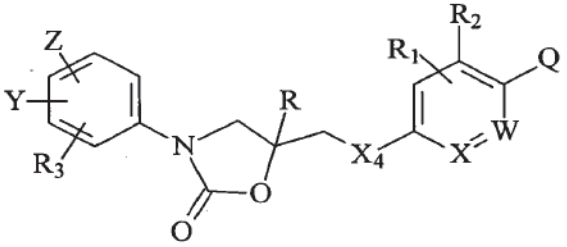
其中 X、$X_4$、Z、Y、Q、$R_1$、$R_2$ 和 $R_3$ 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供式 XLIII 的化合物：



XLIII

在一个实施方案中，本发明提供式 XLIV 的化合物：



XLIV

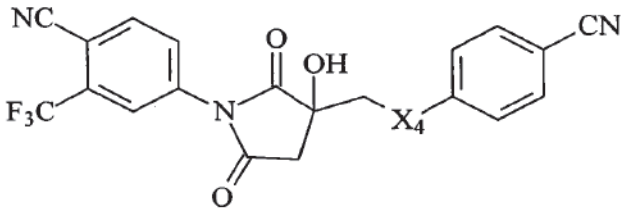
其中：

X、$X_4$、R、$R_1$、$R_2$、$R_3$、Z、Y 和 Q 如以上在化合物 XXXIXV 中所述；

其中

如果 X 是 C，$X_4$ 是 O、NH 或 S，$R_1$、$R_2$ 和 $R_3$ 是 H 并且 R 是 H，那么 Q 不是卤素、H 或 CN。

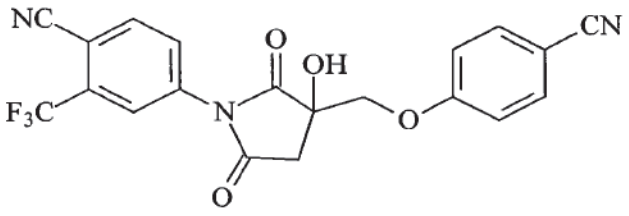
在一个实施方案中，本发明提供由式 XLV 的结构表示的化合物：



XLV

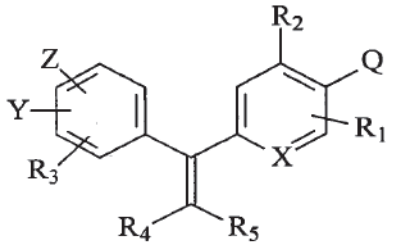
其中 $X_4$ 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供由式 XLVI 的结构表示的化合物：



XLVI

在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



XLVII

I

其中

X 是 N 或 CH；

Z 是 H、CN、$NO_2$、$NHC(O)CH_3$、$CH_3$、F、Cl、I 或 Br；

Y 是 H、$CH_3$、$CF_3$、CN、F、Cl、I 或 Br；

Q 是 H、$O-(CH_2)_2CH(CH_3)_2$ 或 $O-(CH_2)_2N(CH_3)_2$；

$R_1$ 是 H、OH、F、Cl、Br 或 I；

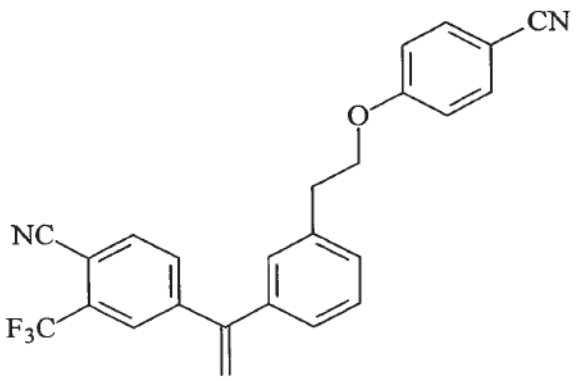
$R_2$ 是由 $R_6$ 取代的苄基、$(CH_2)_2$-O-对氰基苯基、$CH_2$-O-对氰基苯基或 CH=CH-O-对氰基苯基；

$R_3$ 是 H、$CH_3$、卤化物、CN 或 $NO_2$；

$R_4$ 和 $R_5$ 独立地是 H、$CH_3$、卤化物、OH、$C_{1-4}$ 烷基、$C_{1-6}$ 环烷基、卤代($C_{1-4}$ 烷基)、苯基、芳基、杂环或羟基-$C_{1-4}$ 烷基；并且

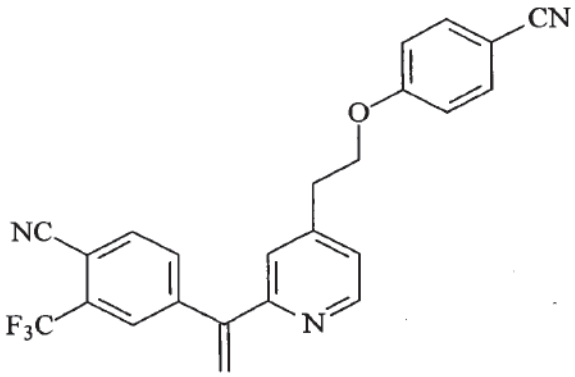
$R_6$ 是 CN、$NO_2$、$NHC(O)CH_3$ 或卤化物。

在一个实施方案中，本发明提供由式 XLVIII 的结构表示的化合物：



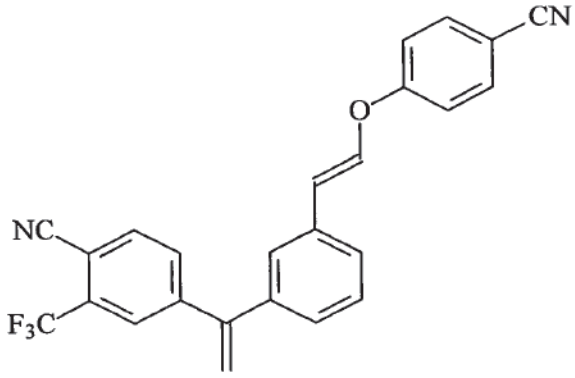
XLVIII

在一个实施方案中，本发明提供由式 XLIX 的结构表示的化合物：



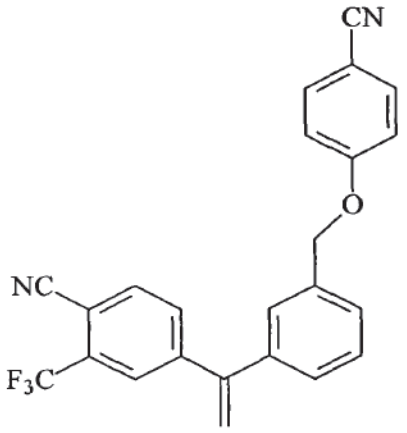
XLIX

在一个实施方案中，本发明提供由式 L 的结构表示的化合物：



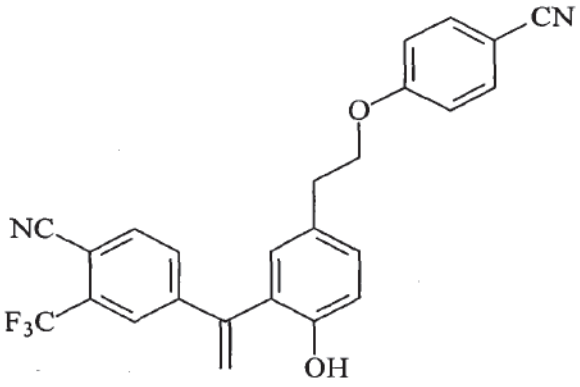
L

在一个实施方案中，本发明提供由式 LI 的结构表示的化合物：



LI

在一个实施方案中，本发明提供由式 LII 的结构表示的化合物：



LII

在另一个实施方案中，本发明提供式 (I)化合物的药学上可接受的盐。在另一个实施方案中，本发明提供式 (I)化合物的药品。在另一个实施方案中，本发明提供式 (I)化合物的水合物。在另一个实施方案中，本发明提供式 (I)化合物的 *N*-氧化物。在另一个实施方案中，本发明提供式 (I)化合物的多晶形物。在另一个实施方案中，本发明提供式 (I)化合物的晶体。在另一个实施方案中，本发明提供式(I)化合物的任意的代谢产物、异构体、药学上可接受的盐、药品、多晶形物、晶体、不纯物（impurity）、水合物、*N*-氧化物的组合。

在一些实施方案中，术语“异构体”包括但不限于光学异构体和类似物、结构异构体和类似物、构象异构体和类似物等。在一个实施方案中，术语“异构体”是指包括所述化合物的光学异构体。本领域的技术人员会理解，本发明的化合物含有至少一个手性中心。因此，在本发明的方法中所使用的化合物可以以光学活性形式或外消旋形式存在或被分离。一些化合物也可以

表现为同质多晶。应该理解，本发明包括任意的外消旋形式、光学活性形式、多晶型形式或立体异构形式、或者它们的混合物，这些形式具有用于治疗本文所述的雄激素相关病症的性质。在一个实施方案中，所述化合物是纯(*R*)-异构体。在另一个实施方案中，所述化合物是纯(*S*)-异构体。在另一个实施方案中，所述 SARM 是所述(*R*)-异构体和(*S*)-异构体的混合物。在另一个实施方案中，所述 SARM 是包含等量的所述(*R*)-异构体和(*S*)-异构体外消旋混合物。如何制备光学活性形式是本领域公知的（例如，通过重结晶技术拆分所述外消旋形式、通过由光学活性原料合成、通过手性合成或通过使用手性固定相进行色谱分离）。

在另一个实施方案中，本发明的化合物是所述(*R*)-异构体和所述(*S*)-异构体的混合物。在另一个实施方案中，所述混合物包含 60%的所述(*R*)-异构体和 40%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 40%的所述(*R*)-异构体和 60%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 70%的所述(*R*)-异构体和 30%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 30%的所述(*R*)-异构体和 70%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 80%的所述(*R*)-异构体和 20%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 20%的所述(*R*)-异构体和 80%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 90%的所述(*R*)-异构体和 10%的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 10%的所述(*R*)-异构体和 90%的所述(*S*)-异构体。

在一个实施方案中，本发明的化合物是 SARM。在一个实施方案中，本发明的化合物与细胞核激素受体例如雌激素受体、孕酮受体或糖皮质激素受体结合。

本发明包括本发明化合物的“药学上可接受的盐”，其可以通过本发明的化合物与酸或碱反应产生。

合适的式 I 的胺的药学上可接受的盐可以由无机酸或有机酸制备。在一个实施方案中，胺的无机盐的例子是硫酸氢盐、硼酸盐、溴化物、氯化物、半硫酸盐（hemisulfates）、氢溴酸盐、盐酸盐、2-羟乙基磺酸盐（羟乙基磺酸盐（hydroxyethanesulfonates））、碘酸盐、碘化物、异硫代硫酸盐（isothionates）、硝酸盐、过硫酸盐、磷酸盐、硫酸盐、氨基磺酸盐、

磺胺酸盐、磺酸（烷基磺酸盐、芳基磺酸盐、卤代烷基磺酸盐、卤代芳基磺酸盐）、磺酸盐和硫氰酸盐。

在一个实施方案中，胺的有机盐的例子包括脂肪族类、脂环族类、芳香族类、芳香脂肪族（araliphatic）类、杂环族类、羧酸类和磺酸类有机酸，它们的例子是乙酸盐、精氨酸、天冬氨酸盐、抗坏血酸盐、己二酸盐、邻氨基苯甲酸盐、链烷羧酸盐、取代链烷羧酸盐、藻酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、丁酸盐，碳酸氢盐、酒石酸氢盐、羧酸盐、柠檬酸盐、樟脑酸盐（camphorates）、樟脑磺酸盐、环己基氨基磺酸盐、环戊烷丙酸盐、依地酸钙盐、右旋樟脑磺酸（camsylates）、碳酸盐、克拉微酸钾、肉桂酸盐、二羧酸盐、二葡糖酸盐、十二烷基磺酸盐、二氢氯化物、癸酸盐、庚酸盐（enanthuates）、乙磺酸盐、乙二胺四乙酸盐、乙二磺酸盐、丙酸酯十二烷基硫酸盐（estolates）、乙磺酸盐、富马酸盐、甲酸盐、氟化物、半乳糖醛酸盐、葡糖酸盐、谷氨酸盐、乙醇酸盐（glycolates）、葡糖酸盐、葡糖庚酸盐（glucoheptanoates）、甘油磷酸盐、葡庚糖酸盐、对羟乙酰氨基苯砷酸盐（glycollylarsanilates）、戊二酸盐、谷氨酸盐、庚酸盐、己酸盐、羟基马来酸盐、羟基羧酸、己基间苯二酚盐（hexylresorcinates）、羟苯酸盐、羟基萘甲酸盐、氢氟酸盐（hydrofluorate）、乳酸盐、乳糖酸盐（lactobionates）、月桂酸盐、苹果酸盐、马来酸盐、亚甲基双（β-萘酚酸盐）(methylenebis(beta-oxynaphthoate))、丙二酸盐、扁桃酸盐、甲磺酸盐（mesylates）、甲磺酸盐（methane sulfonates）、甲基溴化物、甲基硝酸盐、甲基磺酸盐、马来酸单钾盐、粘酸盐、单羧酸盐、萘磺酸盐、2-萘磺酸盐、烟酸盐、萘磺酸盐、*N*-甲基葡糖胺、草酸酯、辛酸盐、油酸盐、双羟萘酸盐、苯乙酸盐、苦味酸盐、苯基苯甲酸盐、新戊酸盐、丙酸盐、邻苯二甲酸盐、果胶酸盐（pectinates）、苯丙酸盐、棕榈酸盐、泛酸盐、多半乳糖醛酸盐（polygalacturates）、丙酮酸盐、奎尼酸盐、水杨酸、琥珀酸盐、硬脂酸盐、磺胺酸盐、碱式醋酸盐、酒石酸、茶碱乙酸盐（theophyllineacetates）、对甲苯磺酸盐、三氟乙酸盐、对苯二酸盐、单宁酸盐、8-氯茶碱盐、三卤代乙酸盐、三乙基碘、三羧酸盐、十一酸盐或者戊酸盐。

在一个实施方案中，羧酸或酚的无机盐的例子包括铵；碱金属，包括

锂、钠、钾、铯；碱土金属，包括钙、镁、铝；锌、钡、氯或季铵。

在另一个实施方案中，羧酸或酚的有机盐的例子包括精氨酸；有机胺，包括脂肪族有机胺、脂环族有机胺、芳香族有机胺、苄星青霉素、叔丁胺、苯乙苄胺(*N*-苄基苯乙胺)、二环己基胺、二甲胺、二乙醇胺、乙醇胺、乙二胺、海巴胺（hydrabamine）、咪唑、赖氨酸、甲胺、三聚氰胺（meglamines）、*N*-甲基-D-葡糖胺、*N*,*N*'-二苄基乙二胺、烟酰胺、有机胺、鸟氨酸、吡啶、甲基吡啶（picolies）、哌嗪、普鲁卡因、三（羟甲基）甲胺、三乙胺、三乙醇胺、三甲胺、氨基丁三醇或尿素。

在一个实施方案中，所述盐可以通过常规方法形成，例如在其中所述盐不溶解的溶剂或介质或者例如水的溶剂中，使产物的游离碱或游离酸形式与一或多当量合适的酸或碱反应来形成，在真空中、通过冷冻干燥或通过将存在的盐的离子交换为另一种离子或合适的离子交换树脂来除去所述盐。

在一个实施方案中，本发明还包括本文所述化合物的氨基取代物的 *N*-氧化物。同样地，可以用脂肪族和芳香族的羧酸制备酚类化合物的酯，例如乙酸酯和苯甲酸酯。

本发明提供所述化合物的衍生物。在一个实施方案中，“衍生物”包括但不限于醚类衍生物、酸类衍生物、酰胺类衍生物、酯类衍生物等。在另一个实施方案中，本发明还包括所述化合物的水合物。

在一个实施方案中，“水合物”包括但不限于半水化合物、一水合物、二水合物、三水合物等。

在另一些实施方案中，本发明提供所述化合物的代谢产物。在一个实施方案中，“代谢产物”指通过代谢或代谢过程由另一种物质产生的任何物质。

在另一些实施方案中，本发明提供所述化合物的药品。在另一些实施方案中，术语“药品”指例如如本文所述的适合制药用途的组合物（药物组合物）。

在一个实施方案中，“烷基”指饱和脂肪族烃，包括直链、支链和环状烷基。在一个实施方案中，所述烷基具有 1-12 个碳原子。在另一个实施方案中，所述烷基具有 1-7 个碳原子。在另一个实施方案中，所述烷基具有

1-6 个碳原子。在另一个实施方案中，所述烷基具有 1-4 个碳原子。所述烷基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代(thio)和硫烷基。在一个实施方案中，所述烷基是 $CH_3$。

在另一个实施方案中，“烯基”指不饱和的烃，包括具有一个或多个双键的直链、支链和环状基团。所述烯基可以具有一个双键、两个双键、三个双键等。烯基的例子是乙烯基、丙烯基、丁烯基、环己烯基等。在一个实施方案中，所述烯基具有 1-12 个碳原子。在另一个实施方案中，所述烯基具有 1-7 个碳原子。在另一个实施方案中，所述烯基具有 1-6 个碳原子。在另一个实施方案中，所述烯基具有 1-4 个碳原子。所述烯基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代和硫烷基。

“卤代烷基”指被一个或多个卤素原子取代的如上定义的烷基，在一个实施方案中被 F 取代，在另一个实施方案中被 Cl 取代，在另一个实施方案中被 Br 取代，在另一个实施方案中被 I 取代。

“芳基”指具有至少一个碳环芳族基团或杂环芳族基团的芳族基团，所述芳基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代和硫烷基。芳环的非限制性的例子是苯基、萘基、吡喃基、吡咯基、吡嗪基、嘧啶基、吡唑基、吡啶基、呋喃基、苯硫基、噻唑基、咪唑基、异噁唑基等。在一个实施方案中，所述芳基是 4-8 元环。在另一个实施方案中，所述芳基是 4-12 元环。在另一个实施方案中，所述芳基是 6 元环。在另一个实施方案中，所述芳基是 5 元环。在另一个实施方案中，所述芳基是 2-4 个环的稠环体系。

“羟基”指 OH 基。本领域的技术人员应该理解，当 T 是 OR 时，R 不是 OH。

在一个实施方案中，术语“卤素”在一个实施方案中指 F，在另一个实施方案中指 Cl，在另一个实施方案中指 Br，在另一个实施方案中指 I。在

一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明的外消旋化合物的分离包括结晶技术。在另一个实施方案中，所述结晶技术包括对映异构体的分异结晶（differential crystallization）。在另一个实施方案中，所述结晶技术包括非对映的盐（酒石酸盐或奎宁盐）的分异结晶。在另一个实施方案中，所述结晶技术包括手性辅助衍生物（薄荷醇酯等）的分异结晶。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明的外消旋化合物的分离包括使所述外消旋混合物与另一种手性基团反应，形成非对映的混合物，然后分离非对映异构体并除去其它手性基团以得到纯的对映异构体。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括手性合成。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括生物拆分。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括酶法拆分。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括使用手性固定相的色谱分离。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括亲和色谱法。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括毛细管电泳。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括形成手性碳原子的羟基与光学活性的酸（例如(-)-樟脑酸）的酯基，通过分级结晶或优选通过快速色谱法（flash-chromatography）分离由此获得的非对映异构体的酯，然后将各单独的酯水解为醇。

在另一个实施方案中，通过本发明的方法或通过本发明的外消旋混合物的手性分离所获得的对映异构体的纯度和选择性可以通过 HPLC 分析来测定。

在另一个实施方案中，所述方法还包含将式(I)的化合物转化为其异构体、代谢产物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合的步骤。

应该理解，所述方法可以包括本文所述的任何实施方案，本领域的技

术人员会理解，所述实施方案会适于制备对应式的化合物。

在一些实施方案中，本文所述的化合物用于预防和治疗肌萎缩症、骨相关的病症和与糖尿病相关的病症。

在一些实施方案中，本文所述的化合物可单独地或作为组合物用于治疗雄性和雌性的各种激素相关的病症，例如性腺功能减退症、少肌症、勃起障碍、缺乏性欲、骨质疏松症和能育性（fertility）。在一些实施方案中，本文所述的化合物用于刺激或促进或恢复对多种过程的功能，这继而导致治疗本文所述的病症，尤其包括促进红细胞生成、骨发生、肌肉生长、葡萄糖摄取、胰岛素分泌，和/或预防脂质生成、凝血、胰岛素抵抗、动脉粥样硬化、破骨细胞活性等。

在一个实施方案中，本发明的方法利用所述化合物与受体接触或结合，并由此介导所述的效应。在一些实施方案中，所述受体是核受体，在一个实施方案中，所述核受体是雄激素受体，或者在另一个实施方案中是雌激素受体，或者在另一个实施方案中是孕酮受体，或者在另一个实施方案中是糖皮质激素受体。在一些实施方案中，所述多种效应可以作为与个体的多种受体结合的功能而同时发生。在一些实施方案中，本文所述的化合物的组织选择性效应提供对不同靶器官的同时作用。

**药物组合物**

在一些实施方案中，本发明提供使用的方法，所述方法包括给药含有所述化合物的组合物。如本文使用的，“药物组合物”指“治疗有效量”的活性成分（即式I的化合物），与药学上可接受的载体或稀释剂。如本文使用的，“治疗有效量”指对于给定的病症和给药方案提供疗效的量。

如本文使用的，术语“给药”指使个体与本发明的化合物接触。如本文使用的，给药可以在体外（即试管内）或体内（即活的有机体例如人类的细胞或组织）中进行。在一个实施方案中，本发明包括向个体给药本发明的化合物。

含有本发明化合物的药物组合物可以通过本领域技术人员已知的任何方法向个体给药，例如口服、肠胃外、血管内、癌旁、经粘膜、经皮、肌内、鼻内、静脉内、皮内、皮下、舌下、腹膜内、心室内、颅内、阴道内给药，通过吸入、经直肠、瘤内给药，或者通过其中重组病毒/组合物能被

递送至组织的任何方法（例如穿刺针（needle）或导管）给药。或者，对于向粘膜细胞施用、皮肤或眼睛施用，可能需要局部施用。另一种给药的方法是经吸入剂或气雾剂。

在一个实施方案中，所述药物组合物口服给药，因此它被配制成适合口服给药的形式，即作为固体或液体制剂。合适的固体口服制剂包括片剂、胶囊、丸剂、颗粒剂、小丸（pellets）、散剂等。合适的液体口服制剂包括溶液剂、混悬剂、分散剂、乳剂、油剂等。在本发明的一个实施方案中，所述 SARM 化合物被配制在胶囊中。根据该实施方案，本发明的组合物除含有本发明的化合物和惰性载体或稀释剂之外，还含有硬胶囊。

在一个实施方案中，所述微粒化的胶囊包含含有本发明化合物的颗粒，其中，本文使用的术语“微粒化”指粒径小于 100 微米的颗粒，或者在另一个实施方案中，指粒径小于 60 微米的颗粒，或者在另一个实施方案中，指粒径小于 36 微米的颗粒，或者在另一个实施方案中，指粒径小于 16 微米的颗粒，或者在另一个实施方案中，指粒径小于 10 微米的颗粒，或者在另一个实施方案中，指粒径小于 6 微米的颗粒。

而且，在另一个实施方案中，所述药物组合物通过静脉内、动脉内或肌内注射液体制剂来给药。合适的液体制剂包括溶液剂、混悬剂、分散剂、乳剂、油剂等。在一个实施方案中，所述药物组合物经静脉内给药，因此被配制成适合静脉内给药的形式。在另一个实施方案中，所述药物组合物经动脉内给药，因此被配制成适合动脉内给药的形式。在另一个实施方案中，所述药物组合物肌内给药，因此被配制成适合肌内给药的形式。

而且，在另一个实施方案中，所述药物组合物局部施用于身体表面，因此被配制成适合局部施用的形式。合适的局部制剂包括凝胶剂、软膏、乳剂、洗剂、滴剂等。对于局部施用，本发明的化合物或其生理上耐受的衍生物（例如盐、酯、*N*-氧化物等）被制成在具有或不具有药用载体的生理上可接受的稀释剂中的溶液剂、混悬剂或乳剂，并以这些形式施用。

而且，在另一个实施方案中，所述药物组合物作为栓剂（例如直肠栓剂或尿道栓剂）来给药。而且，在另一个实施方案中，所述药物组合物通过皮下埋植小丸来给药。在另一个实施方案中，所述小丸在一段时间内提供本文所述化合物的控制释放。在另一个实施方案中，所述药物组合物经

阴道给药。

在另一个实施方案中，活性化合物可以在小囊泡、特别是脂质体中递送(参见Langer, Science 249:1627-1633 (1990); Treat等人,于Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein和Fidler (著者), Liss, New York, pp. 363-366 (1989); Lopez-Berestein, 出处同上, pp. 317-327; 一般地参见出处同上)。

如本文使用的，“药学上可接受的载体或稀释剂”是本领域技术人员熟知的。所述载体或稀释剂可以是用于固体制剂的固体载体或稀释剂、用于液体制剂的液体载体或稀释剂、或它们的混合物。

固体载体/稀释剂包括但不限于胶质、淀粉（例如玉米淀粉、预糊化淀粉（pregeletanized starch））、糖（例如乳糖、甘露醇、蔗糖、葡萄糖）、纤维素材料（例如微晶纤维素）、丙烯酸酯（例如聚甲基丙烯酸酯）、碳酸钙、氧化镁、滑石或它们的混合物。

在一个实施方案中，本发明的组合物可以包括本发明的化合物或其与一种或多种药学上可接受的赋形剂任意组合。

应该理解，本发明包括本文所述化合物（在一些实施方案中被称为“本发明的化合物”）的任何实施方案。

根据本发明的实施方案，合适的赋形剂和载体可以是固体或液体，其类型一般根据使用的给药类型来选择。脂质体也可以用于递送所述组合物。合适的固体载体的例子包括乳糖、蔗糖、明胶和琼脂。口服剂型可以含有合适的粘合剂、润滑剂、稀释剂、崩解剂、着色剂、调味剂、流动诱导剂（flow-inducing agent）和熔解剂。液体剂型可以含有例如合适的溶剂、防腐剂、乳化剂、助悬剂、稀释剂、甜味剂、增稠剂和熔解剂。肠胃外和静脉内形式还应该包含矿物质和其它材料以便使得它们与所选的注射或递药系统的类型相容。当然，也可以使用其它赋形剂。

对于液体制剂，药学上可接受的载体可以是含水的或非水溶液、悬浮液、乳液或油。非水性溶剂的例子是丙二醇、聚乙二醇和可注射的有机酯类例如油酸乙酯。含水载体包括水、醇/水溶液、环糊精、乳液或悬浮液，包括盐水和缓冲介质。油的例子是石油、动物油、植物油或合成来源的油，例如，花生油、大豆油、矿物油、橄榄油、向日葵油和鱼肝油。

肠胃外载体（用于皮下、静脉内、动脉内或肌内注射）包括氯化钠溶液、林格氏葡萄糖、葡萄糖和氯化钠、乳酸林格和固定油。静脉内载体包括流体和营养补充剂、电解质补充剂（例如基于林格氏葡萄糖的电解质补充剂）等。其例子是无菌液体，例如加入和未加入表面活性剂和其它药学上可接受的助剂的水和油。通常，水、盐水、葡萄糖水溶液和相关的糖溶液以及二醇例如丙二醇或聚乙二醇是优选的液体载体，特别是对于可注射溶液剂。油的例子是石油、动物油、植物油或合成来源的油，例如，花生油、大豆油、矿物油、橄榄油、向日葵油和鱼肝油。

而且，所述组合物还可以包含粘合剂（例如阿拉伯胶、玉米淀粉、明胶、卡波姆、乙基纤维素、瓜尔胶、羟丙基纤维素、羟丙基甲基纤维素、聚维酮），崩解剂(例如玉米淀粉、马铃薯淀粉、藻酸、二氧化硅、交联羧甲基纤维素钠（croscarmelose sodium）、交聚维酮、瓜尔胶、羟基乙酸淀粉钠)，各种 pH 和离子强度的缓冲剂(例如 Tris-HCl、醋酸盐、磷酸盐)，防止吸附到表面的添加剂例如白蛋白或明胶，洗涤剂(例如 Tween 20、Tween 80、Pluronic F68、胆汁酸盐)，蛋白酶抑制剂，表面活性剂（例如十二烷基硫酸钠)，渗透促进剂，增溶剂(例如克列莫佛(cremophor)、甘油、聚乙烯甘油(polyethylene glycerol)、苯扎氯铵、苯甲酸苄酯、环糊精、失水山梨糖醇(sobitan)酯、硬脂酸)，抗氧化剂(即抗坏血酸、偏亚硫酸氢钠、丁基化羟基苯甲醚（butylated hydroxyanisole）），稳定剂(例如羟丙基纤维素、羟丙基甲基纤维素)，增黏剂(例如卡波姆、胶体二氧化硅、乙基纤维素、瓜尔胶)，甜味剂(例如天冬甜素、柠檬酸)，防腐剂(例如 Thimerosal、苄醇、对羟苯甲酸酯)，着色剂，润滑剂(例如硬脂酸、硬脂酸镁、聚乙二醇、十二烷基硫酸钠)，助流剂(例如胶体二氧化硅)，增塑剂(例如邻苯二甲酸二乙酯、柠檬酸三乙酯)，乳化剂(例如卡波姆、羟丙基纤维素、十二烷基硫酸钠)，聚合物包衣（例如泊洛沙姆或泊洛沙胺（poloxamines））、包衣剂和成膜剂(例如乙基纤维素、丙烯酸酯、聚甲基丙烯酸酯)和/或辅剂。

在一个实施方案中，本文提供的药物组合物是控释组合物，即在该组合物中，本发明的化合物在给药后的一段时间内释放。控释或缓释组合物包括亲脂性贮库（depots）（例如脂肪酸、蜡、油）中的制剂。在另一个实施方案中，所述药物组合物是速释组合物，即在该组合物中全部量的化合

物在给药后立即释放。

在另一个实施方案中，所述药物组合物可以在控释系统中递送。例如，所述药剂可以使用静脉输注、可植入渗透泵、透皮贴剂、脂质体或其它给药方式给药。在一个实施方案中，可以使用泵(参见 Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald 等人, Surgery 88:607 (1980); Saudek 等人, N. Engl. J. Med. 321:674 (1989))。在另一个实施方案中，可以使用聚合物材料。在另一个实施方案中，可以将控释系统置于治疗靶（即脑）附近，因此仅需要全身剂量的一部分(参见例如 Goodson, 于 Medical Applications of Controlled Release, supra, vol. 2, pp. 116-138 (1984))。在 Langer 的一篇综述 (Science 249:1627-1633 (1990))中讨论了其它控释系统。

所述组合物也可以包括在聚合的化合物，例如聚乳酸、聚乙醇酸、水凝胶等的粉粒制剂之中或之上，或在脂质体、微乳、微胶粒、单层或多层小囊泡、血影或原生质球之上引入活性材料。这种组合物会影响物理状态、溶解性、稳定性、体内释放率和体内清除率。

本发明还包括包被聚合物(例如泊洛沙姆或泊洛沙胺)和与直接抗组织特异性受体、配体或抗原的抗体偶联或与组织特异性受体的配体偶联的化合物的微颗组合物。

本发明还包括通过水溶性聚合物，例如聚乙二醇、聚乙二醇和聚丙二醇的共聚物、羧甲基纤维素、葡聚糖、聚乙烯醇、聚乙烯吡咯烷酮或聚脯氨酸的共价连接而修饰的化合物。已知所述修饰的化合物在静脉注射后显示出比相应的未修饰化合物长得多的血液半衰期（Abuchowski 等人, 1981; Newmark 等人, 1982;和 Katre 等人, 1987）。这种修饰也可以增加所述化合物在水溶液中的溶解度、消除聚集、提高所述化合物的物理和化学稳定性，并大大降低所述化合物的免疫原性和反应性。因此，与未修饰的化合物相比，通过更低频率地或更小剂量地给药这种聚合物-化合物衍生物，可以实现期望的体内生物活性。

含有活性组分的药物组合物的制备在本领域中很好理解，例如通过混合、造粒或压片的方法。活性治疗成分经常与药学上可接受的并与所述活性成分相容的赋形剂混合。对于口服给药，本发明的化合物或它们的生理上耐受的衍生物例如盐、酯、*N*-氧化物等与为此目的惯用添加剂例如载体、

稳定剂或惰性稀释剂混合，并以常规方法转化为适合给药的形式，例如片剂、包衣片剂、硬或软胶囊、水溶液、醇溶液或油溶液剂。对于肠胃外给药，本发明的化合物或它们生理上耐受的衍生物例如盐、酯、*N*-氧化物等被转化为溶液剂、混悬剂或乳剂（如果需要，用为此目的的惯用的、合适的物质，例如增溶剂等）。

活性组分可以作为中性的药学上可接受的盐的形式被配制成组合物。药学上可接受的盐包括酸加成盐（由多肽或抗体分子的自由氨基形成），其由无机酸例如盐酸或磷酸、或有机酸例如乙酸、草酸、酒石酸、扁桃酸等形成。由自由羧基形成的盐也可以得自无机碱，例如氢氧化钠、氢氧化钾、氢氧化铵、氢氧化钙或氢氧化铁，以及有机碱，例如异丙胺、三甲胺、2-乙胺基乙醇、组氨酸、普鲁卡因等。

为了用于药物，所述化合物的盐是药学上可接受的盐。但是，其它盐也可用于本发明化合物或其药学上可接受的盐的制备中。合适的本发明化合物的药学上可接受的盐包括酸加成盐，其可以通过例如将本发明化合物的溶液与药学上可接受的酸的溶液混合来形成，所述酸例如盐酸、硫酸、甲磺酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、草酸、柠檬酸、酒石酸、碳酸或磷酸。

在一个实施方案中，本发明提供包含本发明的化合物的药物组合物。在一个实施方案中，这种组合物用于口服睾酮替代疗法。

在一个实施方案中，本发明还提供包含两种或多种本发明的化合物或它们的多晶型物、异构体、水合物、盐、*N*-氧化物等的组合物。本发明还涉及组合物和药物组合物，所述药物组合物单独包含本发明的化合物，或者包含本发明的化合物与孕激素或雌激素的组合，或者在另一个实施方案中，包含本发明的化合物与化疗化合物、成骨化合物或生肌化合物、或其它适合本文所述的应用的药剂的组合。在一个实施方案中，本发明的组合物包含合适的载体、稀释剂或盐。

在一个实施方案中，本发明的方法可以包括以各种剂量给药本发明的式 I 化合物。在一个实施方案中，以 0.1-200 mg/天的剂量给药本发明的化合物。在一个实施方案中以 0.1-10 mg 的剂量、或在另一个实施方案中以 0.1-26 mg 的剂量、或在另一个实施方案中以 0.1-60 mg 的剂量、或在另一

个实施方案中以 0.3-16 mg 的剂量，或在另一个实施方案中以 0.3-30 mg 的剂量、或在另一个实施方案中以 0.6-26 mg 的剂量、或在另一个实施方案中以 0.6-60 mg 的剂量、或在另一个实施方案中以 0.76-16 mg 的剂量、或在另一个实施方案中以 0.76-60 mg 的剂量、或在另一个实施方案中以 1-6 mg 的剂量、或在另一个实施方案中 1-20 mg 的剂量、或在另一个实施方案中以 3-16 mg 的剂量、或在另一个实施方案中以 30-60 mg 的剂量、或在另一个实施方案中以 30-76 mg 的剂量、或在另一个实施方案中以 100-2000 mg 的剂量给药本发明的化合物。

在一个实施方案中，本发明的方法可以包括以各种剂量给药本发明的式 I 化合物。在一个实施方案中，以 1 mg 的剂量给药本发明的化合物。在另一个实施方案中，以 3 mg、6 mg、10 mg、16 mg、20 mg、26 mg、30 mg、36 mg、40 mg、46 mg、50 mg、56 mg、60 mg、66 mg、70 mg、76 mg、80 mg、86 mg、90 mg、96 mg 或 100 mg 的剂量给药本发明的化合物。

在一个实施方案中，本发明提供使用方法，该方法包括给药包含以下各项的药物组合物：a) 本文所述的任何实施方案的化合物；和 b) 药学上可接受的载体或稀释剂；所述组合物应理解为包含本文所述化合物的类似物、异构体、代谢产物、衍生物、药学上可接受的盐、*N*-氧化物、水合物或它们的任意组合，并且可以包含式 I 的化合物。

在一些实施方案中，本发明提供药物组合物的使用方法，该药物组合物包含：a) 本文所述的任何实施方案的化合物，包括其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合；b) 药学上可接受的载体或稀释剂；c) 助流剂；和 d) 润滑剂。

在另一个实施方案中，本发明提供药物组合物的使用方法，该药物组合物包含：a) 本文所述的任何实施方案的化合物，包括其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合；b) 乳糖一水合物；c) 微晶纤维素；d) 硬脂酸镁；和 e) 胶体二氧化硅。

在一些实施方案中，本发明的方法利用包含本发明的化合物的组合物，所述方法的优点是所述化合物是雄激素受体的非类固醇类配体并在体内显示出合成代谢活性。根据这个方面，这种化合物不伴有严重的副作用，提

供方便的给药方式和较低的生产成本，并且口服可生物利用，与其它不希望的类固醇受体没有显著的交叉反应性，并且可能具有很长的生物半衰期。

当施用于哺乳动物，特别是人时，预计医师会确定最适合个体的实际剂量和治疗时间，并且可以根据具体个体的年龄、体重和应答而变化。

在一个实施方案中，用于给药的组合物可以是无菌溶液剂，或者在其它实施方案中，可以是含水或非水溶液、混悬剂或乳剂。在一个实施方案中，所述组合物可以包含丙二醇、聚乙二醇、可注射的有机酯例如油酸乙酯、或环糊精。在另一个实施方案中，组合物也可以包含湿润剂、乳化剂和/或分散剂。在另一个实施方案中，所述组合物也可以包含无菌水或任何其它无菌可注射介质。

在一个实施方案中，本发明提供用于如本文所述的本发明的任何方法的化合物和组合物（包括本文所述的任意实施方案）。在一个实施方案中，使用本发明的化合物或含有它的组合物会有利于抑制、压制、增强或促进个体体内所期望的应答，这一点本领域的技术人员会理解。在另一个实施方案中，所述组合物还可以含有其它活性成分，其活性对给药本发明的化合物所针对的具体应用是有用的。

在一些实施方案中，本发明的方法利用含有本发明的化合物的组合物，所述方法的优点是所述化合物是雄激素受体的非类固醇类配体并在体内显示出合成代谢活性。根据这个方面，这种化合物不伴有严重的副作用，提供方便的给药方式和较低的生产成本，并且口服可生物利用，与其它不希望的类固醇受体没有显著的交叉反应性，并且可能具有很长的生物半衰期。

当施用于哺乳动物，特别是人时，预计医师会确定最适合个体的实际剂量和治疗时间，并且可以根据具体个体的年龄、体重和应答而变化。

在一个实施方案中，用于给药的组合物可以是无菌溶液剂，或者在其它实施方案中，可以是水性或非水性的溶剂、悬混剂或乳剂。在一个实施方案中，所述组合物可以包含丙二醇、聚乙二醇、可注射的有机酯例如油酸乙酯、或环糊精。在另一个实施方案中，组合物也可以包含湿润剂、乳化剂和/或分散剂。在另一个实施方案中，所述组合物也可以包含无菌水或任何其它无菌可注射介质。

在一个实施方案中，本发明提供用于如本文所述的本发明的任何方法

的化合物和组合物（包括本文所述的任意实施方案）。在一个实施方案中，使用本发明的化合物或含有它的组合物会有利于抑制、压制除、增强或促进个体体内所期望的应答，这一点本领域的技术人员会理解。在另一个实施方案中，所述组合物还可以含有其它活性成分，其活性对给药本发明的化合物所针对的具体应用是有用的。

在一些实施方案中，所述组合物还含有 5α-还原酶抑制剂（5ARI）、一种或多种 SARM、选择性雌激素受体调节剂（SERM）、芳香酶抑制剂（例如但不局限于阿那曲唑（anastrazole）、依西美坦或来曲唑）、GnRH 激动剂或拮抗剂、类固醇或非类固醇 GR 配体、类固醇或非类固醇 PR 配体、类固醇或非类固醇 AR 配体、17-醛酮还原酶抑制剂或 17β-羟基类固醇脱氢酶抑制剂。在一些实施方案中，这种组合物可以用于治疗激素依赖性病症，例如不育、激素反应性癌例如生殖腺癌或泌尿生殖器癌的瘤形成。

在一些实施方案中，所述组合物包含本文所述的化合物和另一种治疗性化合物，尤其包括 5ARI，例如非那雄胺、度他雄胺、艾宗特来；其他 SARM，例如，RU-58642、RU-56279、WS9761 A 和 B、RU-59063、RU-58841、贝氯特来、LG-2293、L-245976、LG-121071、LG-121091、LG-121104、LGD-2226、LGD-2941、LGD-3305、YM-92088、YM-175735、LGD-1331、BMS-357597、BMS-391197、S-40503、BMS-482404、EM-4283、EM-4977、BMS-564929、BMS-391197、BMS-434588、BMS-487745、BMS-501949、SA-766、YM-92088、YM-580、LG-123303、LG-123129、PMCol、YM-175735、BMS-591305、BMS-591309、BMS-665139、BMS-665539、CE-590、116BG33、154BG31、arcarine、ACP-105；SERM，例如，三苯氧胺（tamoxifene）、4-羟三苯氧胺、艾多昔芬、托瑞米芬、奥培米芬（ospemifene）、屈洛昔芬、雷诺昔芬、阿佐昔芬，巴多昔芬（bazedoxifene）、PPT (1,3,5-三(4-羟基苯基)-4-丙基-1*H*-吡唑)、DPN (二芳基丙腈)、拉索昔芬、哌喷昔芬(pipendoxifene)、EM-800、EM-652、萘福昔定、秦哚昔芬、替米利芬、磷酸米泼昔芬、RU 58,688、EM 139、ICI 164,384、ICI 182,780、氯米芬、MER-25、二乙基己烯雌酚、香豆雌酚、染料木黄酮、GW5638、LY353581、珠氯米芬、恩氯米芬（enclomiphene）、地马孕酮醋酸盐、

DPPE、(*N,N*-二乙基-2-{4-(苯基甲基)-苯氧基}乙胺)、TSE-424、WAY-070、WAY-292、WAY-818、cyclocommunol、普林贝瑞(prinaberel)、ERB-041、WAY-397、WAY-244、ERB-196、WAY-169122、MF-101、ERb-002、ERB-037、ERB-017、BE-1060、BE-380、BE-381、WAY-358、[18F]FEDNP、LSN-500307、AA-102、半枝莲(Ban zhi lian)、CT-101、CT-102、VG-101；GnRH 激动剂或拮抗剂，例如，亮丙瑞林、戈舍瑞林、曲普瑞林、阿法前列醇、组氨瑞林、地肽瑞里、加尼瑞克、安肽伊妥瑞克、西曲瑞克、雷莫瑞克、加尼瑞克、安雷利克斯、替维瑞克、阿巴瑞克、奥扎瑞克(ozarelix)、舒伐格瑞克(sufugolix)、普拉瑞克、地加瑞克(degarelix)、NBI-56418、TAK-810、脂酰基碱(acyline)；FSH 激动剂或拮抗剂、LH 激动剂/拮抗剂、芳香酶抑制剂，例如来曲唑、阿那曲唑、阿他美坦、法倔唑、米那美坦、依西美坦、普洛美坦、利阿唑、NKS-01、伏氯唑、YM-51、芬罗唑、4-羟雄烯二酮、氨基苯乙哌啶酮(aminogluethimide)、罗谷亚胺；类固醇或非类固醇糖皮质激素受体配体，例如，ZK-216348、ZK-243149、ZK-243185、LGD-5552、米非司酮、RPR-106541、ORG-34517、GW-215864X、Sesquicillin、CP-472555、CP-394531、A-222977、AL-438、A-216054、A-276575、CP-394531、CP-409069、UGR-07；类固醇或非类固醇孕酮受体配体；类固醇或非类固醇 AR 拮抗剂，例如氟他胺、羟基氟他胺、比卡鲁胺、尼鲁米特，羟基类固醇脱氢酶抑制剂，PPARα配体例如苯扎贝特、非诺贝特、吉非贝齐；PPARγ配体，例如，达格列酮、吡格列酮、罗格列酮、伊格列酮(isaglitazone)、利格列酮（rivoglitazone）、萘格列酮（netoglitazone）；双重作用的 PPAR 配体，例如，naveglitazar、法格立他扎、替格列扎(tesaglitazar)、拉格列扎(ragaglitazar)、奥格列扎(oxeglitazar)、PN-2034、PPAR δ；17-酮还原酶抑制剂，3β-DHΔ4,6-异构酶抑制剂，3β-DHΔ4,5-异构酶抑制剂，17,20 碳链酶抑制剂，p450c17 抑制剂，p450ssc 抑制剂，17,20 裂合酶抑制剂，或它们的组合。

应该理解，以上给药两种或多种药剂的任何方法、计时、途径或它们的组合应被认为由本文所述的短语“联合给药”所包含。

在一个实施方案中，本发明提供患癌个体的骨骼相关事件(SRE)的治

疗、预防、压制或抑制、或降低罹患它的风险，其包括给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合，所述骨骼相关事件(SRE)例如骨折、骨手术、骨辐射、脊髓压迫症、新生骨转移、骨丢失或它们的组合。本发明特别涉及用式(I)的化合物治疗正在进行或已经进行雄激素剥夺治疗(ADT)的罹患前列腺癌个体的 SRE。

在一个实施方案中，用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件是骨折，在一个实施方案中，所述骨折是病理性骨折、非创伤性骨折、脊椎骨折、非脊椎骨折、形态测定骨折（morphometric fractures）或它们的组合。在一些实施方案中，骨折可以是闭合骨折、复合骨折、横骨折、青枝骨折或粉碎性骨折。在一个实施方案中，发生骨折的可以是身体的任何骨，在一个实施方案中，所述骨折是臂、腕、手、指、腿、踝、足、趾、髋、锁骨的任意一块或多块骨中的骨折或它们的组合。

在另一个实施方案中，本文提供的方法和/或组合物有效地治疗、预防、压制、抑制骨骼相关事件、或降低其风险，所述骨骼相关事件例如病理性骨折、脊髓压迫症、高钙血症多、骨相关的疼痛或它们的组合。

在另一个实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括必要的骨手术和/或骨辐射，其在一些实施方案中，用于治疗在一个实施方案中由骨损害或神经压迫引起的疼痛。在另一个实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括个体的脊髓压迫症，或有必要改变抗肿瘤疗法，包括改变激素疗法。在一些实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括治疗、压制、预防骨转移或骨丢失、降低其发病率或延缓其进展或严重性。在一个实施方案中，骨丢失可以包括骨质疏松症、骨质减少或它们的组合。在一个实施方案中，骨骼相关事件可以包括本文所列的实施方案的任意组合。

在一个实施方案中，本文提供的方法和/或利用本文提供的组合物有效地减少骨转移，例如在病灶数量、病灶大小或它们的组合方面。根据本发明的这一方面，在一个实施方案中，本文提供一种预防或抑制个体癌症向骨转移的方法，所述包括向所述个体给药包含托瑞米芬、雷洛昔芬、他莫

昔芬或其类似物、功能衍生物、代谢产物或它们的组合、或它们的药学上可接受的盐的组合物的步骤。在一个实施方案中，所述代谢产物可以包括奥培米芬、非培米芬（fispemifene）或它们的组合。在一个实施方案中，所述癌症是前列腺癌。

在一个实施方案中，所述骨骼相关事件是癌症治疗的结果。在一个实施方案中，所述骨骼相关事件是激素剥夺治疗的结果，而在另一个实施方案中，它们是雄激素剥夺治疗(ADT)的结果。

在一个实施方案中，本发明的化合物用于预防或逆转雄激素剥夺治疗(ADT)引起的副作用，例如肌肉量减少、肌肉强度降低、脆弱、性腺功能减退症、骨质疏松症、骨质减少、BMD 降低和/或骨量减少。

在雄性，尽管成熟期性激素的自然下降（雄激素直接减少以及由雄激素的外周芳构化产生的雌激素的低水平）与骨脆弱有关，但是这种效应在已接受雄激素剥夺治疗的雄性更明显。

在一些实施方案中，本发明的任意组合物包含任意形式的或本文所述的任意实施方案中的式 I 化合物。在一些实施方案中，本发明的任意组合物由任意形式的或在本文所述的任意实施方案中的式 I 化合物组成。在一些实施方案中，本发明的任意组合物主要由任意形式的或在本文所述的任意实施方案中的式 I 的化合物组成。在一些实施方案中，术语“包含”指包含所指的活性剂（例如式 I 的化合物）以及包含制药产业中已知的其它活性剂和药学上可接受的载体、赋形剂、润滑剂、稳定剂等。在一些实施方案中，术语“主要由...组成”指这样的组合物，其唯一的活性成分是所指的活性成分，但是，可以包括用于制剂的稳定、保存等的其它化合物，但是所述其它化合物不直接参与所指的活性成分的疗效。在一些实施方案中，术语“主要由...组成”可以指促进所述活性成分的释放的组分。在一些实施方案中，术语“由...组成”指含有所述活性成分和药学上可接受的载体或赋形剂的组合物。

在一个实施方案中，本发明提供联合制剂。在一个实施方案中，术语“联合制剂”特别地定义为“药盒(kit of parts)”，其意思是如以上定义的组合搭档可以独立地给药，或者通过使用具有不同量的组合搭档的不同的固定组合物给药，即同时地、并发地、分别地或依次地给药。那么，在一些实施方

案中，所述药盒的部件例如可以同时给药，或者按时间先后交替（即对于药盒任何部件在不同的时间点，以相同或不同的时间间隔）给药。在一些实施方案中，可以控制所述联合制剂中的组合搭档的总量的比率。在一个实施方案中，例如为了应对部分待治疗患者亚群的需要或单个患者的需要，所述组合制剂可以变化，所述不同的需要可能归因于具体疾病、所述疾病的严重性、年龄、性别或体重，这可以由本领域的技术人员容易地确定。

应该理解，本发明涉及用于任何适当的疾病、障碍或病症的本文所述的组合物和联合疗法，本领域的技术人员会意识到这一点。上文叙述了所述组合物和联合疗法对特定疾病、障碍和病症的某些应用，它们代表本发明的实施方案，而通过单独或作为所述联合疗法的部分来给药本文所述的化合物或使用本发明的组合物来治疗个体的所述疾病、障碍和病症的方法代表本发明其他的实施方案。

选择性雄激素调节剂化合物的生物活性

在一些实施方案中，本发明的化合物可以用于口服睾酮替代疗法。在其它实施方案中，适当取代的化合物用于：a) 男性避孕；b) 治疗各种激素相关的病症，例如与 ADAM 相关的病症，例如疲劳、抑郁、性欲降低、性功能障碍、勃起功能障碍、性腺功能减退症、骨质疏松症、脱发、肥胖症、少肌症、骨质减少、良性前列腺增生以及情绪和认知改变；c) 治疗与 ADIF 有关的病症，例如性功能障碍、性欲降低、性腺功能减退症、少肌症、骨质减少、骨质疏松症、认知和情绪变化、抑郁、贫血、脱发、肥胖症、子宫内膜异位症、乳腺癌、子宫癌和卵巢癌；d) 治疗和/或预防慢性肌萎缩；e) 治疗前列腺癌、前列腺癌成像、降低前列腺癌的发病率、使其中止或导致其消退；f) 治疗 I 型糖尿病；g) 治疗 II 型糖尿病；h) 压制或抑制糖尿病或降低其发病率；i) 治疗葡萄糖耐受不良；j) 治疗高胰岛素血症；k) 治疗胰岛素抵抗；l) 治疗糖尿病肾病；m) 治疗糖尿病神经病变；n) 治疗糖尿病视网膜病变；o) 治疗脂肪肝症；p) 治疗恶病质；q) 口服雄激素替代和/或其它临床治疗和/或诊断领域，包括本文所述的术语“治疗”所包括的任何实施方案。

在一些实施方案中，本发明的化合物在体内具有组织选择性雄激素活性和合成代谢活性，因此，可用于具体应用，本领域的技术人员会所意识

到这一点。

在一个实施方案中，本发明提供：a) 治疗罹患肌萎缩症的个体的方法；b) 治疗罹患营养不良的个体的方法；c) 治疗个体的骨相关病症的方法；d) 增加个体骨量的方法；e) 改善个体脂质分布的方法；f) 治疗动脉粥样硬化及其相关疾病的方法；g) 改善个体的灵活性和运动的方法；h) 治疗罹患侏儒症的个体的方法；i) 治疗罹患痛经的个体的方法；j) 治疗罹患精神性性交困难的个体的方法；k) 治疗罹患精子生成障碍性不育的个体的方法；这些方法包括向所述个体给药式 I 的化合物和/或所述化合物的类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、不纯物或晶体或它们的任意组合。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于各种应用和治疗其中需要改善认知、减少或治疗抑郁或其它神经保护作用的疾病。

在一个实施方案中，“认知”指认识的过程，特别是保持清醒、认识、思维、学习和判断的过程。认知涉及心理学、语言学、计算机科学、神经科学、数学、习性学和哲学领域。在一个实施方案中，“情绪”指脾气或精神状态。如本文所指的，变化指认知和/或情绪的任何积极或消极变化。

在一个实施方案中，“抑郁”指涉及身体、情绪和思维的疾病，其影响人吃饭、睡觉的方式、自我感知的方式和考虑事物的方式。抑郁的体征和症状包括缺乏活动兴趣、食欲缺乏或进食过量、缺乏表情、空虚、感觉绝望、悲观、内疚或无助、社交退缩（social withdrawal）、疲劳、睡眠障碍、集中、记忆或作决定困难、躁动、易怒、头痛、消化障碍或慢性疼痛。

在一个实施方案中，本发明的方法用于个体，其为人类。在另一个实施方案中，所述个体是哺乳动物。在另一个实施方案中，所述个体是动物。在另一个实施方案中，所述个体是无脊椎动物。在另一个实施方案中，所述个体是脊椎动物。

在一个实施方案中，所述个体是雄性。在另一个实施方案中，所述个体是雄性。在一些实施方案中，尽管本文所述的方法可以用于治疗雄性和雌性，但是，如本文所述和所举例的，对于某些方法，雌性更有利地应答某些化合物的给药。

在一些实施方案中，尽管本文所述的方法可以用于治疗雄性和雌性，但是，如本文所述的，对于某些方法，雄性更有利地应答某些化合物的给药。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于以下各项的应用或治疗：脱发（hair loss）、脱发（alopecia）、雄激素性脱发、斑秃、继发化学疗法的脱发、继发放射疗法的脱发、由瘢痕形成诱导的脱发或由应激诱导的脱发。在一个实施方案中，“脱发（hair loss）”或“脱发（alopecia）”指如极普遍类型的男人型脱发的脱发。脱发通常由头皮的斑块脱发开始，有时发展至全秃，甚至体毛脱落。脱发既影响男性也影响女性。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与罹患贫血的个体相关的疾病或病症的应用和治疗。在一个实施方案中，“贫血”指具有小于血液中红血细胞的正常数量或小于血液中血红蛋白的正常量、血细胞比容降低、或平均血细胞体积减小或血细胞尺寸减小的病症。在贫血时，血液的携氧能力下降。在一些实施方案中，治疗贫血在本文中也可以指治疗导致贫血的潜在因素，例如：a) 出血；b) 溶血（红血细胞过度破坏）；c) 红血细胞产生不足；和 d) 正常血红蛋白不足。在一些实施方案中，本发明的治疗贫血指治疗贫血的任何形式，包括再生障碍性贫血、苯中毒、范科尼贫血、新生儿溶血病、遗传性球形红细胞增多症、缺铁性贫血、骨质疏松症、恶性贫血、再生障碍性贫血、溶血性贫血、镰状细胞贫血、肾性贫血、地中海贫血、骨髓增生异常综合征和各种骨髓疾病。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与个体的性欲问题或个体的勃起功能障碍有关的疾病和/或病症的应用和/或治疗。在一个实施方案中，“性欲”可以指性本能。

在一个实施方案中，术语“勃起”指竖立或直立的能力。勃起组织是能够通过其含有的大量血管的膨胀而极大地膨胀并变硬的组织。

在本发明的另一个实施方案中，提供用于个体（即罹患雄激素依赖性病症的个体）的激素治疗的方法，所述方法包括使患者的雄激素受体与本发明的化合物和/或非类固醇激动剂和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合接触的步骤，上述化合物的量有效地使其与所述雄激素受体结合并实现改变雄激素依赖性病症。

在本发明的一个实施方案中，提供用于患者（即罹患雄激素依赖性病症的个体）激素替代治疗的方法，所述方法包括向个体给药足以实现改变所述个体的激素依赖性病症的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症包括与衰老、性腺功能减退症、少肌症、红细胞生成减少、骨质疏松症和与低雄激素（例如睾酮）或雌激素水平相关的任意的其它病症相关的病症。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症可以包括以雄激素或雌激素水平升高为特征的病症，包括多毛症、不育、多囊卵巢综合征、子宫内膜癌、乳腺癌、男人型脱发、前列腺癌、睾丸癌等，本领域的技术人员会知道这一点。对于这些病症，可以向所述个体单独地或联合其它治疗剂给药本文所述的化合物，本领域的技术人员会理解这一点。

在一个实施方案中，本发明提供治疗个体的癌症、降低其发病率、严重性或发病、延缓其进展、延长缓解期或延缓其发作的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。在一些实施方案中，这些癌症是与雄性或雌性的生殖组织相关的激素依赖性或雄激素受体依赖性肿瘤（恶性或良性的），例如前列腺癌、卵巢癌、乳腺癌、子宫癌或睾丸癌等。

在一些实施方案中，本发明提供治疗个体癌前前兆或病变、降低其发病率的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。在一些实施方案中，这些癌前前兆是见于激素应答组织中的雄激素受体依赖性肿瘤或是与雄性或雌性的生殖组织例如前列腺、卵巢、乳腺、子宫或睾丸等相关。在一些实施方案中，这些癌前前兆包括例如前列腺、子宫颈等的任何局部的上皮内瘤样病变。在一些实施方案中，这种方法用于治疗在例如雄性或雌性生殖组织

的组织中的瘤或肿瘤前期、发育异常或增生。

在一个实施方案中，本发明提供化合物、组合物和/或它们在治疗良性前列腺增生(BPH)中的使用方法。“BPH（良性前列腺增生）”是前列腺的良性增大，它是在任何内脏器官中发现的最普通的良性增生性异常，并且是成年男性发病的主要病因。超过 75%的大于 50 岁的男性患 BPH，在九十岁的男性中，其患病率达到 88%。BPH 经常导致逐渐挤压穿过前列腺的尿道部分（前列腺尿道）。因为膀胱的不完全排空和尿急，这造成患者尿频急。尿流的梗阻也能导致一般的排尿失控，包括当希望排尿时排尿启动困难以及因为不能从膀胱排空尿而造成阻止尿流困难（一种称为充溢性尿失禁（overflow urinary incontinence）的病症，它可以导致尿路梗阻和泌尿衰竭（urinary failure））。

在本发明的一个实施方案中，治疗个体的良性前列腺增生(BPH)的方法包括向所述个体给药有效治疗所述个体的 BPH 的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。

在一些实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗个体的恶病质和/或与癌症有关的恶病质、减轻其严重性、降低其发病率或减少其发病的使用方法。在另一个实施方案中，所述癌症包括肾上腺皮质癌、直肠癌、膀胱癌、脑瘤、脑干胶质瘤、脑瘤、小脑星形细胞瘤、大脑星形细胞瘤（cerebral astrocytoma）、室管膜瘤、髓母细胞瘤、幕上原始神经外胚叶瘤（supratentorial primitive neuroectodermal）、松果体瘤、下丘脑胶质瘤、乳腺癌、类癌瘤、癌、子宫颈癌、结肠癌、结直肠癌、子宫内膜癌、食管癌、肝外胆管癌、尤文家族肿瘤（ewings family of tumors）(Pnet)、颅外胚细胞肿瘤、眼癌、眼内黑色素瘤、胆囊癌、胃癌、胚细胞瘤、性腺外肿瘤、妊娠滋养细胞肿瘤、头颈癌、下咽癌、胰岛细胞癌、喉癌、白血病、急性淋巴细胞性白血病、口腔癌、肝癌、肺癌、非小细胞肺癌、小细胞肺癌、AIDS 相关的淋巴瘤、中枢神经系统（原发性）淋巴瘤、皮肤 T 细胞淋巴瘤、淋巴瘤（霍奇金病和非霍奇金病）、恶性间皮瘤、黑色素瘤、Merkel 细胞癌、转移性鳞癌、多发性骨髓瘤、浆细胞瘤、蕈样肉芽肿病、骨髓增生异常综合征、骨髓增殖性疾病、鼻咽癌、神经

母细胞瘤、口咽癌、骨肉瘤、卵巢上皮样癌、卵巢生殖细胞肿瘤、卵巢低恶性潜在肿瘤、胰腺外分泌癌（exocrine pancreatic cancer）、胰岛细胞癌、胰腺癌、鼻旁窦和鼻腔癌、甲状旁腺癌、阴茎癌、嗜铬细胞瘤癌、垂体癌、浆细胞瘤、前列腺癌、横纹肌肉瘤、直肠癌、肾细胞癌、涎腺癌、塞扎里综合征、皮肤癌、皮肤T细胞淋巴瘤、卡波西肉瘤、黑色素瘤、小肠癌、软组织肉瘤、软组织肉瘤、睾丸癌、恶性胸腺瘤、甲状腺癌、尿道癌、子宫癌、肉瘤、童年期异常癌、阴道癌、外阴癌、肾母细胞瘤或它们的任意组合。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗肺癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗非小细胞肺癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗霍奇金病（或者在另一个实施方案中，非霍奇金病）、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗结直肠癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在一些实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗癌症、减轻其严重性、降低其发病率或减少其发病的用途。在另一个实施方案中，所述癌症包括雄激素AR依赖性肿瘤（恶性或良性的），例如前列腺癌、乳腺癌（男性或女性、可行手术或不能手术的）。在另一个实施方案中，所述SARM化合物是

ADT 的辅药（adjunct），所述 ADT 用于治疗前列腺癌、膀胱癌、脑癌、骨肿瘤、结肠癌、子宫内膜癌、肝癌、肺癌、淋巴癌、肾癌、骨肉瘤癌、卵巢癌、胰腺癌、阴茎癌、皮肤癌、甲状腺癌和/或激素依赖性癌。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：a) 治疗骨相关的病症；b) 预防骨相关的病症；c) 压制骨相关的病症；d) 抑制骨相关的病症；e) 增加个体的骨强度；f) 增加个体的骨量；g) 抑制破骨细胞形成的用途。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：a) 加速骨修复；b) 治疗骨病症；c) 治疗骨密度降低；d) 治疗低骨矿物质密度(BMD)；e) 治疗骨量减少；f) 治疗代谢骨病；g) 促进骨生长或再生；h) 促进骨恢复；i) 促进骨折修复；j) 促进骨重建；k) 治疗成形外科（包括脸部、髋部或关节的）后的骨损害；l) 提高骨强度和功能；m) 增加骨皮质量；n) 增加小梁连接性。

在一个实施方案中，所述骨相关的病症是遗传性病症，在另一个实施方案中，是由特定疾病的治疗方案诱导的结果。例如，在一个实施方案中，本文所述的化合物用于治疗由癌症向骨转移而引起的骨相关的病症，或在另一个实施方案中，治疗例如由给予雄激素剥夺治疗应答个体的前列腺致癌作用而引起的骨相关的病症。

在一个实施方案中，所述骨相关的病症是骨质疏松症。在另一个实施方案中，所述骨相关的病症是骨质减少。在另一个实施方案中，所述骨相关的病症是骨吸收增加。在另一个实施方案中，所述骨相关的病症是骨折。在另一个实施方案中，所述骨相关的病症是骨脆弱。

在另一个实施方案中，所述骨相关的病症是骨矿物质密度(BMD)丢失。在另一个实施方案中，所述骨相关的病症是骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱和 BMD 丢失的任意组合。每种病症代表本发明独立的实施方案。

在一个实施方案中，“骨质疏松”指由于钙和骨蛋白的消耗造成的骨变薄和骨量减少。在另一个实施方案中，骨质疏松症是全身性的骨骼疾病，其特

征是骨量低、骨组织退化，并由此导致骨脆弱和骨折易感性增加。在骨质疏松症患者，骨强度是异常的，在一个实施方案中，伴随由此引起的骨折风险增加。在另一个实施方案中，骨质疏松症使通常在见于骨中的钙和蛋白质胶原流失，在一个实施方案中，这导致骨性质异常或骨密度下降。在另一个实施方案中，受骨质疏松症影响的骨可仅仅由于通常不会造成骨折的轻微跌倒或损伤而骨折。在一个实施方案中，骨折可以是裂纹骨折的形式（如在髋骨折中）或压缩性骨折的形式（如在脊椎压迫性骨折中）。脊柱、髋和腕是骨质疏松诱发骨折的通常部位，但是，骨折也可以发生于其它骨骼部位。在另一个实施方案中，未加抑制的骨质疏松能够导致体位的改变、身体异常和灵活性下降。

在一个实施方案中，所述骨质疏松症由雄激素剥夺引起。在另一个实施方案中，所述骨质疏松症在雄激素剥夺后发生。在另一个实施方案中，所述骨质疏松症是原发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是继发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是绝经后骨质疏松症。在另一个实施方案中，所述骨质疏松症是幼年骨质疏松症。在另一个实施方案中，所述骨质疏松症是特发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是老年性骨质疏松症。

在另一个实施方案中，所述原发性骨质疏松症是 I 型原发性骨质疏松症。在另一个实施方案中，所述原发性骨质疏松症是 II 型原发性骨质疏松症。每种类型的骨质疏松症代表本发明的独立的实施方案。

根据本发明的这一方面，在一个实施方案中，用本文所述的化合物或其组合治疗所述骨相关的病症。在另一个实施方案中，在给药本文所述的一种或多种化合物之前、同时或之后，可以提供给个体其它骨促进性化合物。在一个实施方案中，所述骨促进性化合物可以包括天然的或合成的物质。

在一个实施方案中，所述骨促进性化合物可以包括骨形态生成蛋白(BMP)；生长因子，例如表皮生长因子(EGF)、成纤维细胞生长因子(FGF)、转化生长因子(TGF)、胰岛素生长因子(IGF)、血小板源性生长因子(PDGF)；Hedgehog 蛋白（例如 *sonic* hedgehog、*indian* hedgehog 和 *desert* hedgehog）；激素，例如促卵泡激素、甲状旁腺素、甲状旁腺激素相关肽、激活素、抑制素、滤泡抑素、*frizzled* 蛋白、*frzb* 蛋白或 *frazzled* 蛋白；BMP 结合蛋白，例

如脊索蛋白和胎球蛋白；细胞因子，例如 IL-3、IL-7、GM-CSF；趋化因子，例如嗜酸细胞活化趋化因子；胶原；骨钙蛋白；骨黏连蛋白等；本领域的技术人员会理解这一点。

在另一个实施方案中，本发明用于治疗骨病的组合物可以包含本文所述的一种或多种化合物、额外的一种或多种骨促进性化合物和骨原细胞。在一个实施方案中，骨原细胞可以是可以被诱导分化为成骨细胞的干细胞或祖细胞。在另一个实施方案中，所述细胞可以是成骨细胞。在另一个实施方案中，可以向个体给药编码骨促进性化合物的核酸，这应该被认为是本发明的部分。

在一个实施方案中，本发明的方法包括含给药用于治疗骨质疏松症的化合物。在另一个实施方案中，本发明的方法包括给药化合物（与 SERM 联合），用于治疗骨质疏松症。在另一个实施方案中，所述 SERM 是三苯氧胺、4-羟三苯氧胺、艾多昔芬、托瑞米芬、奥培米芬、屈洛昔酚、雷诺昔芬、阿佐昔芬、巴多昔芬、PPT (1,3,5-三(4-羟基苯基)-4-丙基-1*H*-吡唑)、DPN (二芳基丙腈)、拉索昔芬、哌喷昔芬、EM-800、EM-652、萘福昔定、秦哚昔芬、替米利芬、磷酸米泼昔芬、RU 58,688、EM 139、ICI 164,384、ICI 182,780、氯米芬、MER-25、二乙基己烯雌酚、香豆雌酚、染料木黄酮、GW5638、LY353581、珠氯米芬、恩氯米芬、地马孕酮醋酸盐、DPPE、(*N,N*-二乙基-2-{4-(苯基甲基)-苯氧基}乙胺)、TSE-424、WAY-070、WAY-292、WAY-818、cyclocommunol、普林贝瑞、ERB-041、WAY-397、WAY-244 ERB-196、WAY-169122、MF-101、ERb-002、ERB-037、ERB-017、BE-1060、BE-380、BE-381、WAY-358、[18F] FEDNP、LSN-500307、AA-102、半枝莲、CT-101、CT-102、VG-101。

在另一个实施方案中，本发明的方法包括与二膦酸盐联合给药所述 SARM 化合物用于治疗骨质疏松症，所述二膦酸盐例如阿屈膦酸盐、替鲁膦酸（tiludroate）、氯屈膦酸钠（clodroniate）、帕米磷酸钠、羟乙膦酸盐、阿屈膦酸盐、唑屈膦酸盐（zolendronate）、英卡膦酸二钠（cimadronate）、奈立膦酸钠（neridronate）、米诺膦酸（minodronic acid）、依班膦酸盐、利塞膦酸盐或 homoresidronate。

在另一个实施方案中，本发明的方法包括与降钙素例如鲑精组蛋白

（salmon）、依降钙素、SUN-8577 或 TJN-135 联合给药所述化合物用于治疗骨质疏松症。

在另一个实施方案中，本发明的治疗骨质疏松症的方法包括联合以下物质给药所述 SARM 化合物：a) 维生素 D 或衍生物，例如 ZK-156979；b) 维生素 D 受体配体和类似物，例如骨化三醇、钙三醇(topitriol)、ZK-150123、TEI-9647、BXL-628、Ro-26-9228、BAL-2299、Ro-65-2299 或 DP-035；c) 雌激素、雌激素衍生物或结合型雌激素；d) 抗雌激素药、孕激素或合成雌激素/孕激素；e) RANK 配体单克隆抗体，例如 denosumab(以前称为 AMG162 (Amgen))；f) αvβ3 整合素受体拮抗剂；g) 破骨细胞空泡型 ATP 酶抑制剂；h) 结合 VEGF 的破骨细胞受体拮抗剂；i) 钙受体拮抗剂；j) PTh（甲状旁腺素）和类似物、PTHrP 类似物（甲状旁腺素相关肽）；k) 组织蛋白酶 K 抑制剂（AAE581 等）；l) 雷尼酸锶；m) 替勃龙；n) HCT-1026、PSK3471；o) 麦芽糖镓（gallium maltolate）；p) Nutropin AQ；q) 前列腺素（用于骨）；r) p38 蛋白激酶抑制剂；s) 骨形态生成蛋白；t) BMP 拮抗抑制剂；u) HMG-CoA 还原酶抑制剂；v) 维生素 K 或衍生物；w) 依普黄铜；x) 氟化盐；y 饮食钙补充剂和 z) 骨保护素。

在一个实施方案中，本发明的方法用于治疗由激素紊乱、破坏或不平衡引起的或与之相关的疾病或病症。在一个实施方案中，所述激素紊乱、破坏或不平衡包括激素过量。在另一个实施方案中，所述激素紊乱、破坏或不平衡包括激素缺乏。在一个实施方案中，所述激素是类固醇激素。在另一个实施方案中，所述激素是雌激素。在另一个实施方案中，所述激素是雄激素。在另一个实施方案中，所述激素是糖皮质激素。在另一个实施方案中，所述激素是皮质类固醇。在另一个实施方案中，所述激素是黄体生成素（LH）。在另一个实施方案中，所述激素是促卵泡激素（FSH）。在另一个实施方案中，所述激素是本领域已知的任何其它激素。在另一个实施方案中，所述激素紊乱、破坏或不平衡与绝经有关。在另一个实施方案中，所述激素紊乱、破坏或不平衡与男性更年期、男性更年期血管舒缩综合征、男性更年期乳腺发育、肌肉强度和/或功能下降、骨强度和/或功能下降和发怒有关。在另一个实施方案中，激素缺乏是特定处理的结果，如治疗个体疾病或病症的副产物。例如，所述激素缺乏可以是作为个体前列腺癌疗法的雄激素消耗的结果。

每种可能性代表本发明的独立的实施方案。

在另一个实施方案中，本发明涉及治疗少肌症或恶病质和与其相关的病症（例如骨疾病或病症）。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：1) 治疗肌萎缩症；2)预防肌萎缩症；3) 治疗、预防、压制、抑制或减少归因于肌萎缩症引起的肌肉损失；4) 治疗、预防、抑制、减少或压制归因于肌萎缩症的肌萎缩；和/或 5) 治疗、预防、抑制、减少或压制归因于肌萎缩症的肌肉蛋白分解代谢；和/或治疗、预防、抑制、减少或压制归因于终末期肾脏疾病或 CKD 的肌萎缩；和/或 6) 治疗、预防、抑制、减少或压制脆弱。

在另一个实施方案中，用于治疗罹患肌萎缩症或本文所述的任何病症的个体的化合物的用途包括给药包含本文所述的化合物的药物组合物。在另一个实施方案中，所述给药步骤包括将液体形式的所述药物组合物经静脉内、动脉内或肌内注射给所述个体；在所述个体体内皮下埋植含有所述药物组合物的小丸；口服向所述个体给药液体或固体形式的所述药物组合物；或向所述个体的皮肤表面局部施用所述药物组合物。

肌肉是主要用作动力源的身体组织。身体的肌肉有三种类型：a) 骨骼肌——负责身体的四肢和外部区域运动的肌肉；b) 心肌——心脏肌肉；和 c) 平滑肌——位于动脉和肠壁中的肌肉。

在本文中，消耗性（wasting）病症或障碍定义为至少部分地以体重、器官质量或组织质量的异常的进行性损失为特征的病症或障碍。消耗性病症可以作为疾病例如癌症或感染的结果而发生，或可归因于生理或代谢状态，例如因长期卧床休息或当肢体被固定（例如在铸型中）时发生的废用性失调。消耗性病症也可以是年龄相关的。在消耗性病症过程中发生的体重减少的特征可以是总体重的减少或器官重量的减少，例如归因于组织蛋白减少的骨量或肌肉量的减少。

在一个实施方案中，如本文交替使用的，“肌萎缩（muscle wasting）”或“肌萎缩（muscular wasting）”指肌肉量的进行性损失和/或肌肉的进行性衰减和退化，包括控制运动的骨骼肌或随意肌和控制心脏的心肌和平滑肌。在一

个实施方案中，所述肌萎缩病症或障碍是慢性肌萎缩病症或障碍。“慢性肌萎缩”在本文中定义为肌肉量的慢性（即持续很长一段时间的）进行性损失和/或肌肉的慢性进行性衰减和退化。

肌萎缩过程中发生的肌肉量损失可以是以由于肌肉蛋白分解代谢造成的肌肉蛋白分解或降解为特征。蛋白质分解代谢因为异常高速的蛋白质降解、异常低速的蛋白质合成或这两种的结合而发生。无论是由高度的蛋白质降解还是低度的蛋白质合成引起的肌肉蛋白分解代谢或消耗都会导致肌肉量的减少和肌萎缩。术语“分解代谢”具有本领域中普遍知晓的含义，特别是指能量燃烧形式的新陈代谢。

肌萎缩可以作为病状、疾病、病症或障碍的结果而发生。在一个实施方案中，所述病状、疾患、疾病或病症是慢性的。在另一个实施方案中，所述病状、疾患、疾病或病症是遗传性的。在另一个实施方案中，所述病状、疾患、疾病或病症是神经的。在另一个实施方案中，所述病状、疾患、疾病或病症是感染性的。如本文所述的，为之给药本发明的化合物和组合物的病状、疾病、病症或障碍是直接或间接产生肌肉量的消耗（即损失），即肌萎缩症的疾病。

在一个实施方案中，个体的肌萎缩由所述个体的肌营养不良症、肌萎缩、伴 X 染色体的脊延髓肌萎缩症（SBMA）引起。

所述肌营养不良症是遗传性疾病，其特征是控制运动的骨骼肌或随意肌的进行性衰减和退化。心脏肌肉和一些其它不随意肌也受到某些形式的肌营养不良的影响。肌营养不良（MD）的主要形式是：迪谢内肌肉营养不良、强直性肌营养不良、迪谢内肌肉营养不良、贝克肌营养不良、肢肌营养不良、面肩胛臂肌营养不良、先天性营养不良症、眼咽肌营养不良、远侧肌营养不良和埃-德二氏肌营养不良。

肌营养不良症可以影响所有年龄的人群。尽管某些形式首先在婴儿或儿童中出现，其它可能直到中年或更晚才出现。迪谢内 MD 是最普通的形式，一般影响儿童。强直性肌营养不良是这些疾病中在成人中的最通常的疾病。

肌萎缩（MA）以肌肉的消耗或减少和肌肉量的减少为特征。例如，小儿麻痹症后期 MA 是作为小儿麻痹小儿麻痹症后期综合征（PPS）的一部分而发生的肌肉萎缩。所述萎缩包括虚弱、肌疲劳和疼痛。

其它类型的MA是伴X染色体的脊延髓肌萎缩症(SBMA,也称为Kennedy病)。该病由X染色体上的雄激素受体基因的缺陷引起,仅影响男性,其在成年期发作。因为主要病因是雄激素受体突变,所以雄激素替代不是流行的治疗策略。有一些调查研究,其中给予外源性丙酸睾酮以提高雄激素的水平,这有希望克服雄激素不敏感性并可能提供合成代谢效应。然而,使用超生理水平的睾酮用于补充会有局限性和其它潜在的严重并发症。

少肌症是折磨老人和慢性病患者的使人衰弱的疾病,其特征是肌肉量和功能的损失。而且,瘦体重的增加与某些肌萎缩症的发病率和死亡率降低有关。而且,其它情况和病症也与肌萎缩症有联系并能导致肌萎缩。例如,有研究显示,在慢性下腰痛的严重病例中,出现椎旁肌萎缩。

肌萎缩和其它组织消耗也与高龄有关。相信,在老年人中,全身虚弱归因于肌萎缩。随着身体的老化,更多比例的骨骼肌被纤维组织代替。结果,肌肉的力量、性能和耐力显著下降。

由于疾病或损伤而长期住院或例如当肢体被固定时发生的废用性失调也能导致肌肉萎缩或其它组织消耗。研究显示,在长期住院的罹患损伤、慢性病、烧伤、创伤或癌症的患者中,出现长期单侧肌萎缩和体重减少。

中枢神经系统(CNS)损伤或损害也与肌肉萎缩和其它消耗性病症有关。CNS损伤或损害可由例如疾病、创伤或化学药品引起。其例子有中枢神经损伤或损害、周围神经损伤或损害和脊髓损伤或损害。在一个实施方案中,CNS损害或损伤包括阿尔茨海默氏病(AD)、发怒(情绪)、厌食症、神经性厌食症、与衰老有关的厌食症和/或自信(情绪)。

在另一个实施方案中,肌萎缩和其它组织消耗可能由酒精中毒引起,可以用本发明的化合物和组合物来治疗,这代表它们的实施方案。

在一个实施方案中,本发明提供本文所述的化合物或其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗个体的消耗性疾病、障碍或病症的用途。

在一个实施方案中,所述被治疗的消耗性疾病、障碍或病症与慢性病有关。

在一些实施方案中,本发明涉及治疗可能在肌萎缩、体重减少、营养不

良、饥饿中表现出的任何消耗性病症、或任何归因于组织量减少的功能消耗或缺失。

在一些实施方案中，消耗性疾病或病症，例如恶病质、营养不良、结核病、麻风病、糖尿病、肾脏病、慢性障碍性肺病（COPD）、癌症、终末期肾衰竭、少肌症、肺气肿、骨软化症或心肌病，可以通过本发明的方法，经给药本文所述的 SARM 化合物、包含它的组合物、附加或不附加为所治疗的病症提供疗效的药物、化合物或药剂来治疗。

在一些实施方案中，消耗是由于感染肠道病毒、Epstein-Barr 病毒、带状疱疹、HIV、锥虫、流感（influenze）、柯萨奇病毒、立克次氏体、旋毛虫、血吸虫或分枝杆菌，在一些实施方案中，本发明提供其治疗方法。

恶病质是由疾病引起的或作为疾病副反应的虚弱和体重减少。心原性恶病质，即心肌和骨骼肌的肌肉蛋白消耗，是充血性心力衰竭的特征。癌症恶病质是发生在患有实体瘤和恶性血液病的患者的综合征，其表现为因脂肪组织和瘦肌肉量的大量消耗而导致的体重减少。

恶病质也见于获得性免疫缺陷综合征（AIDS），人类免疫缺陷病毒（HIV）相关肌病和/或肌无力/肌萎缩是 AIDS 比较通变的临床表现。患有 HIV 相关肌病或肌无力/肌萎缩的个体通常经受严重的体重下降、全身的或近端的肌无力、压痛和肌萎缩。

在一些实施方案中，本发明提供用于治疗个体感染、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药包含化合物和免疫调节剂、抗感染剂、基因治疗剂或它们的组合的组合物免疫调节剂。在一个实施方案中，所述抗感染剂可以是抗真菌剂、抗细菌剂、抗病毒剂、或抗寄生虫剂或它们的组合。在一些实施方案中，感染包括放射菌病、边虫病、炭疽、曲霉病、菌血症、细菌真菌病、巴尔通体感染、肉毒中毒、布氏菌病、伯霍尔德杆菌感染、弯曲杆菌传染、念珠菌病、猫抓病、衣原体传染、霍乱、梭菌感染、球孢子菌病、交叉感染、隐球菌病、皮肤真菌病、白喉病、埃里希体病、大肠杆菌感染、坏死性筋膜炎、梭杆菌感染、气性坏疽、革兰氏阴性细菌感染、革兰氏阳性细菌感染、组织胞浆菌病、脓疱病、克雷伯菌感染、军团杆菌病、麻风病、钩端螺旋体病、利斯特菌感染、莱姆病、马杜拉分支菌病、类鼻疽、分枝杆

菌感染、支原体感染、真菌病、诺卡尔菌感染、甲癣、瘟疫、肺炎球菌感染、假单胞菌感染、鹦鹉热、Q 热、鼠咬热、回归热、风湿热、立克次体感染、洛基山斑点热、沙门菌感染、猩红热、恙虫热斑疹伤寒、败血症、性传播疾病、葡萄球菌感染、链球菌感染、破伤风、蜱传播性疾病(tick-borne diseases)、结核病、土拉菌病、伤寒、虱传斑疹伤寒、弧菌感染、雅司病、耶尔森菌感染、人兽互通病、接合菌病、获得性免疫缺陷综合征、腺病毒科感染、甲病毒感染、虫媒病毒传染、Borna 病、布尼亚病毒科感染、嵌杯病毒科感染、水痘、冠状病毒科感染、柯萨奇病毒感染、巨细胞病毒感染、登革热、DNA 病毒感染、触染性痘疮、脑炎、虫媒病毒、Epstein-barr 病毒感染、传染性红斑、汉坦病毒感染、出血热、病毒性肝炎、病毒性人单纯疱疹、带状疱疹、耳部带状疱疹、疱疹病毒科感染、传染性单核细胞增多症、人拉沙热、麻疹、传染性软疣、流行性腮腺炎、副粘病毒科感染、白蛉热、多瘤病毒感染、狂犬病、呼吸合胞体病毒感染、裂谷热、RNA 病毒感染、风疹、慢病毒疾病、天花、亚急性硬化性全脑炎、肿瘤病毒感染、疣、西尼罗热、病毒性疾病、黄热病、阿米巴病、异尖线虫病、蛔虫病、巴贝虫病、人芽囊原虫感染、臭虫叮咬、绦虫感染、美洲锥虫病、隐孢子虫病、环孢子虫感染、囊虫病、双核阿米巴病、裂头绦虫病、龙线虫病、包虫病、体外寄生虫感染、丝虫病、贾第虫病、蠕虫病、钩虫感染、幼虫移行症、利什曼病、虱寄生、罗阿丝虫病、疟疾、感染、蝇蛆病、盘尾丝虫病、原虫感染、疥疮、血吸虫病、(寄生虫性)皮肤病、类圆线虫病、绦虫病、弓蛔虫病、弓形体病、旋毛虫病、滴虫感染、锥虫病、非洲锥虫病或者鞭虫感染。

在一些实施方案中，本发明提供用于治疗个体肌骨疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药或它们的组合。在一些实施方案中，肌骨疾病包括软骨发育不全、获得性骨肥大综合征、尖头并指（趾）畸形、关节炎、关节挛缩、关节病、神经原性滑囊炎、软骨疾病、锁骨颅骨发育不良、畸形足、筋膜间隔综合征、颅面骨发育不全、颅缝早闭、皮肌炎、杜普伊特伦氏挛缩、侏儒症、埃-范二氏综合征、内生软骨瘤病、酸

细胞增多性肌痛综合征、外生骨疣、筋膜炎、疲劳综合征、纤维肌痛、骨纤维性结构不良、多骨纤维性结构不良、扁平足、足畸形、弗莱尔伯格二蹠骨远端缺血坏死、漏斗胸、Goldenhar 综合征、痛风、拇外翻、髋脱位、骨肥厚、椎间盘移位、歌舞伎化妆综合征(kabuki make-up syndrome)、克-费二氏综合征、兰-吉综合征、莱-佩二氏病、脊柱前凸、下颌骨颜面发育不全、肢骨纹状肥大、线粒体肌病、肌痛性痉挛、肌痉挛状态、肌营养不良、肌肉骨骼畸形、肌骨疾病、肌炎、骨化性肌炎、肌管性肌病、畸形性骨炎、骨性关节炎、骨软骨炎、成骨不全、骨髓炎、骨坏死、骨硬化症、骨质疏松症、波伦综合征、复发性多软骨炎、风湿性多肌痛、多肌炎、横纹肌溶解、风湿性疾病、鲁-辛二氏综合征、绍伊尔曼氏病、脊柱侧凸、塞佛氏病/跟骨骨突炎、脊柱疾病、脊髓骨赘病、椎管狭窄、强直性脊柱炎、脊椎前移、施普伦格耳畸形、滑膜炎、肌腱病变、网球肘、腱鞘炎、致死性发育不全或 Tietze 综合征。

在一些实施方案中，本发明提供用于治疗个体的消化系统疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗胃肠系统的药、抗感染药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，胃肠疾病包括腺瘤结肠息肉、Alagille综合征、肛门疾病、阑尾炎、巴雷特食管、胆道闭锁、胆道疾病、卡罗利病、乳糜泻、胆管炎、胆囊炎、胆石症、溃疡性结肠炎、克罗恩病、吞咽障碍、十二指肠的溃疡、痢疾、假膜性小肠结肠炎、食管失弛症、食管闭锁、食管炎、胰腺外分泌功能不全、脂肪肝、大便失禁、胃炎、肥厚性胃炎、胃肠炎、胃食管反流、胃肌轻瘫、痔疮、肝静脉血栓形成、肝炎、慢性肝炎、膈疝、食管裂孔疝、希尔施普龙病、高血压(HTN)、门静脉高压、炎性肠疾病、肠疾病、肠肿瘤、肠神经元发育异常、肠梗阻、肠易激综合征、乳糖不耐受、肝硬化、肝病、梅克尔憩室、胰腺疾病、胰腺肿瘤、胰腺炎、消化性溃疡、杰格斯综合征、直肠炎、直肠疾病、直肠脱垂、短肠综合征、气管食管瘘、惠普尔病或卓林格-艾丽逊综合征。

在一些实施方案中，本发明提供用于治疗个体口颚病、降低其发病率、

延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，口颚病包括舌系带过短、夜磨牙症、口灼伤综合征、唇炎、巨颌症、唇裂、含牙囊肿、龈炎、良性迁移性舌炎、唇疱疹、路德维希咽峡炎、巨舌、迈-罗二氏综合征、牙周疾病、皮埃尔·罗班综合征、下颌前突、涎腺疾病、流涎、口疮性口炎、颞下颌关节障碍、颞下颌关节功能紊乱综合征或者口干燥症。

在一些实施方案中，本发明提供用于治疗个体的呼吸道疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗心血管系统的药、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，呼吸道疾病包括气道阻塞、呼吸暂停、石棉沉着病、哮喘、哮喘诱导的肌无力或者骨虚弱、肺膨胀不全、铍中毒、支气管疾病、支气管扩张、细支气管炎、闭塞性细支气管炎机化性肺炎、支气管炎、支气管肺发育不良、慢性阻塞性肺病(COPD)、感冒、咳嗽、胸腔积脓、会厌炎、糖皮质激素(GC)引起的肌病或骨质减少、咯血、肺动脉高压、通气过度、卡塔格内综合征、肺脓肿、肺病、胎便吸入综合征、胸腔积液、胸膜炎、肺炎、气胸、肺泡蛋白质沉着症、慢性阻塞性肺病、肺水肿、肺栓塞、肺气肿、肺纤维化、呼吸窘迫综合征、新生儿呼吸过敏症、呼吸道感染、鼻硬结病、弯刀综合征、严重急性呼吸器官综合病、矽肺、睡眠呼吸暂停、中央喘鸣、气管狭窄、归因于哮喘的肌肉量或骨量减少、慢性阻塞性肺病(COPD)中的消耗、韦格纳氏肉芽肿或者百日咳。

在一些实施方案中，本发明提供用于治疗个体耳鼻喉疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，耳鼻喉疾病包括中耳胆脂瘤、哮吼、耳聋、鼻出血、听力损失、听觉过敏、迷路炎、喉炎、喉

软化、喉狭窄、乳突炎、梅尼埃病、鼻塞、鼻息肉、耳炎、耳鼻喉病、耳硬化、咽炎、老年性耳聋、咽后脓肿、鼻炎、鼻窦炎、耳鸣、扁桃体炎、鼓膜穿孔、前庭神经元炎、声带麻痹或者语音障碍。

在一些实施方案中，本发明提供用于治疗个体神经系统疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、治疗中枢神经系统的药、抗感染药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，神经系统疾病包括自主神经系统疾病、中枢神经系统疾病、颅神经疾病、脱髓鞘疾病、神经系统畸形、神经病学表现或神经肌肉疾病。

在一些实施方案中，自主神经系统疾病包括灼性神经痛或反射性交感神经营养障碍。

在一些实施方案中，中枢神经系统疾病包括阿尔茨海默氏病、蛛网膜炎、脑脓肿、脑缺血、中枢神经系统感染、大脑性瘫痪、脑血管障碍、皮质基底节变性(corticobasal ganglionic degeneration, CBGD)、Creutzfeldt-Jakob 综合征、丹-沃二氏综合征、痴呆、脑炎、脑脊髓炎、癫痫症、癫痫症诱导的性腺机能减退和/或代谢增进状态、特发性震颤、弗里德赖希共济失调、杰茨曼-斯脱司勒-史茵克病、哈-斯二氏综合征、亨廷顿病、脑积水、缺氧、失眠、脑缺血发作（ischemic attack）、库鲁病、Landau-Kleffner 综合征、Lewy 体病、马-约病、Meige 综合征、脑膜炎、细菌性脑膜炎、病毒性脑膜炎、偏头痛、运动障碍、多系统萎缩、脊髓炎、橄榄体脑桥小脑萎缩、帕金森病、帕金森障碍、脊髓灰质炎、脊髓灰质炎后综合征、朊病毒病、假脑瘤、希-德二氏综合征、婴儿痉挛、脊髓疾病、核上性麻痹、脊髓空洞症、丘脑疾病、抽搐性运动障碍、多动秽语综合征或葡萄膜脑膜脑炎综合征。在一些实施方案中，所述中枢神经系统疾病是囊性纤维化病诱导的性腺机能减退状态。

在一些实施方案中，颅神经疾病包括 Bell 麻痹、颅神经疾病、面部半侧萎缩、面神经痛、舌咽神经疾病、莫比乌斯综合征或者三叉神经痛。

在一些实施方案中，中枢神经系统疾病包括对中枢神经系统（CNS）的损伤或损害。在一些实施方案中，对 CNS 的损伤或损害可能与肌萎缩症有关。

对 CNS 的损伤或损害可以由例如疾病、创伤或化学试剂引起。其例子是中枢神经损伤或损害、周围神经损伤或损害和脊髓损伤或损害。

涉及脊髓损伤（SCI）患者的研究已经显示，在 SCI 后，中枢神经递质可能会改变，造成下丘脑-垂体-肾上腺轴功能障碍，它的破坏导致睾酮和其它激素水平的严重下降。SCI 或其它急性疾病或创伤特征性地包括分解代谢增强和合成代谢活动减低，导致易于损失瘦身体组织的病症，并经常伴随紊乱的营养利用。瘦体重的损失的影响包括伤口扩展和愈合机制受损，使问题进一步复杂化。由于营养不良和蛋白分解代谢加上固定，脊髓损伤的患者处于高度的患褥疮的风险中。

在一个实施方案中，本发明的方法可以治疗各种 CNS 损伤。在一个实施方案中，CNS 损伤可以指神经细胞膜的分解，或者在另一个实施方案中，指神经不能产生或传播神经冲动，或者在另一个实施方案中，指神经细胞的死亡。损伤包括直接或间接影响 CNS 的正常功机能的损害。所述损伤可能是结构性、物理性或机械性损伤，并可能在挤压、压缩或拉伸神经纤维的情况下由身体冲击造成。或者，所述细胞膜可能因疾病、化合失调或生理功能障碍，例如缺氧（例如卒中）、动脉瘤或再灌注而被破坏或降解。CNS 损伤非限制性地包括例如对视网膜神经节细胞损害、外伤性脑损伤、卒中相关的损伤、脑动脉瘤相关的损伤、脊髓损伤（包括单瘫、双侧瘫痪、截瘫、偏瘫和四肢瘫痪）、神经增殖性病症或神经性疼痛综合征。

由于对哺乳动物脊髓的损伤，脊髓中神经之间的连接断裂。这种损伤阻断受该损伤影响的神经束的神经冲动的流动，结果损害感觉功能和运动功能。对脊髓的损伤可能缘于脊髓的压缩或其它挫伤、脊髓挤压或切断。脊髓切断（本文中也称为“横切”），可能是脊髓的完全切断或可能是不完全切断。

在一些实施方案中，治疗罹患 CNS 损伤（或在另一个实施方案中为罹患脊髓损伤）的个体的方法可能伴随用损伤部位的电刺激和给药嘌呤核苷或其类似物（例如美国专利申请公开 20040214790A1 中所述）治疗所述个体。

在一些实施方案中，脱髓鞘疾病包括肾上腺脑白质营养不良、亚历山大病、卡纳万病、脱髓鞘病、Schilder 弥漫性脑硬化、球形细胞脑白质营养不良、异染性脑白质营养不良、多发性硬化或视神经脊髓炎。

在一些实施方案中，神经系统畸形包括阿-蔡二氏畸形、夏-马-图三氏病、

脑膨出、遗传性运动和感觉性神经病、透明隔-视神经发育不良、隐性脊柱裂或椎管闭合不全。

在一些实施方案中，神经病学表现包括失认症、遗忘症、命名不能症、失语症、失用症、背痛、布朗-塞卡尔综合征、小脑性共济失调、舞蹈症、交流障碍、意识错乱、头晕、诵读困难、张力失常、面神经麻痹、肌束震颤、步态障碍、神经性头痛、偏瘫、记忆障碍、智力低下、缄默症、肌阵挛、颈痛、非语言学习障碍、嗅觉障碍、疼痛、麻痹、幻肢、面容失认症、四肢瘫痪、癫痫发作、痉挛、言语障碍、共同感觉迟发性运动障碍、味觉障碍、斜颈、震颤、牙关紧闭、意识丧失或眩晕。

在一些实施方案中，神经肌肉疾病包括肌萎缩侧索硬化、臂丛神经炎、臂丛神经病、延髓性麻痹、腕管综合征、肘管综合征、糖尿病神经病变、家族性自主神经异常、格-巴二氏综合征、遗传性感觉和自主神经系统神经病、米勒·费希尔综合征、运动神经元病、脊髓性肌萎缩、重症肌无力、先天性结构性肌病、神经卡压综合征、神经痛、神经肌肉疾病、家族周期性麻痹、周围神经系统疾病、POEMS 综合征、多神经病、多发性神经根病、雷夫叙姆病、坐骨神经痛、儿童脊髓性肌萎缩、僵人综合征（stiff-person syndrome）、胸廓出口综合征或尺神经压缩综合征。

在一个实施方案中，治疗罹患神经系统疾病的个体的方法包括治疗所述个体的任何继发性病症，所述病症由所述个体患有神经系统疾病而引起，其中的一些在本文中有叙述。

在一些实施方案中，本发明提供用于治疗个体的眼睛疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、治疗心血管系统的药、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，眼睛疾病包括急性区域性隐匿性外层视网膜病变(acute zonal occult outer retinopathy)、埃迪综合征、白化病、眼睛黑蒙（ocular-amaurosis）、弱视（fugax）、弱视（amblyopia）、无虹膜、瞳孔不等、无眼畸形、无晶状体、散光、睑缘炎、眼睑下垂、睑痉挛、盲、白内障、睑板腺囊肿、脉络膜视网膜炎、无脉络膜、眼缺损、色觉缺陷、结膜炎、角膜疾病、角膜营养不良、角膜水肿、

角膜溃疡、糖尿病视网膜病变、复视、双行睫、干眼综合征、Duane 眼球后退综合征、睑外翻、睑内翻、内斜视、虹膜色素剥脱综合征、外斜视、眼出血、眼睛瘤、眼睑疾病、悬浮物、广泛纤维化综合征(general fibrosis syndrome)、青光眼、环状萎缩、偏盲、血小板病-白化病综合征、睑腺炎、霍纳综合征、远视、前房出血、虹膜炎、Kearns-Sayer 综合征、角膜炎、圆锥角膜、泪器疾病、泪管阻塞、晶体疾病、黄斑变性、小眼、近视、病理性眼震、Kearns-Sayer、动眼神经疾病、眼肌麻痹、视神经萎缩、视神经疾病、视神经炎、视神经病变、眶蜂窝织炎、视神经乳头水肿、Peter 异常、老视、翼状胬肉、瞳孔失调、屈光不正、视网膜脱离、视网膜疾病、视网膜静脉闭塞、视网膜色素变性、早产儿视网膜病、视网膜劈裂症、巩膜炎、暗点、斜视、Thygeson 表层点状角膜炎、沙眼、葡萄膜炎、白点综合征、视觉障碍或者玻璃体病症。

在一些实施方案中，本发明提供治疗个体的泌尿道和/或男性生殖器疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗胃肠系统的药、抗感染药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，泌尿系疾病和/或男性生殖器疾病包括抗肾小球基底膜疾病、阴茎头炎、膀胱外翻、膀胱肿瘤、隐睾症、间质性膀胱炎、肾性尿崩症、附睾炎、富尼埃坏疽、肾小球肾炎、古德帕斯丘综合征、血性精液、血尿、溶血尿毒症综合征、肾盂积水、尿道下裂、阳痿、不育、肾结石、急性肾功能衰竭、慢性肾功能衰竭、急性肾小管坏死、海绵肾、多囊性肾发育不良、遗传性肾炎、肾病、肾病综合征、夜尿、少尿、阴茎疾病、阴茎硬结、阴茎肿瘤、包茎、阴茎异常勃起、前列腺疾病、良性前列腺增生、前列腺肿瘤、蛋白尿、肾盂肾炎、赖特病、肾动脉梗阻、精索扭转、睾丸疾病、尿道狭窄、尿道炎、尿潴留、泌尿道感染、排尿障碍、泌尿道和男性生殖器疾病、泌尿系疾病、精索静脉曲张、膀胱或尿道回流。

在一些实施方案中，本发明提供治疗个体的皮肤病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包含给予个体组合物，所述组合物包含化合物和抗癌药、免疫

调节剂、治疗皮肤病症的药、抗感染药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，皮肤病症包括痤疮、光线性角化病、脱发、雄激素性脱发、斑秃、继发化学疗法的脱发、继发放射疗法的脱发、由瘢痕形成诱导的脱发、应激诱导的脱发、血管瘤、足癣、水源性瘙痒症、特应性皮炎、脱发、早年脱发、男人性脱发、雄激素性脱发、基底细胞癌、烧伤、褥疮、白塞氏病、睑缘炎、疖、Bowen 病、大疱性类天疱疮、复发性口溃疡、痈、组织蜂窝炎、氯痤疮、手脚慢性皮炎、出汗不良症、感冒疮、接触性皮炎、匍行疹、头皮屑、皮炎、疱疹样皮炎、皮肤纤维瘤、尿布疹、湿疹、大疱性表皮松解症、丹毒、红皮病、擦伤水泡、生殖器疣、化脓性汗腺炎、荨麻疹、多汗症、鱼鳞病、脓疱病、边缘性皮霉病、卡波西肉瘤、瘢痕疙瘩、角化棘皮瘤、毛发角化病、虱感染、扁平苔癣、慢性单纯性苔癣、脂肪瘤、淋巴结炎、恶性黑色素瘤、黑斑病、痱、传染性软疣、钱币状皮炎、佩吉特乳头病、虱病、天疱疮、口周皮炎、光变态反应、光过敏、玫瑰糠疹、毛发红糠疹、银屑病、雷诺病、钱癣（ring worm）、酒渣鼻、疥疮、硬皮病、皮脂腺囊肿、脂溢性角化症、脂溢性皮炎、带状疱疹、皮肤癌、皮赘、蜘蛛状血管病、鳞状细胞癌、淤滞性皮炎、蜱叮咬、须癣、头癣、体癣、股癣、脚癣、甲癣、花斑癣、癣、潜蚤病、癜风病或疣。

在一个实施方案中，所述皮肤病症是伤口或烧伤。在一些实施方案中，发现伤口和/或溃疡从皮肤突出或在粘膜表面上或是器官梗死形成的结果。伤口可能是软组织缺损或损害或者潜在疾病的结果。在一个实施方案中，术语“伤口”指具有正常的组织结构完整性的破坏的身体损伤。该术语也包括术语“疮”、“损害”、“坏死”和“溃疡”。在一个实施方案中，术语“疮”指皮肤或粘膜的任何损害，术语“溃疡”指器官或组织表面的局部缺损或陷凹，其由坏死组织的腐离产生。损害一般与任意的组织缺损有关。坏死与由感染、损伤、发炎或梗死形成引起的死亡组织有关。所有这些都由术语“伤口”包括，所述“伤口”指愈合过程中的任意特定阶段的任何伤口，所述阶段包括任何愈合开始前的阶段，或甚至在产生特定伤口（像外科切口）（预防治疗）之前的阶段。

待根据本发明预防和/或治疗的伤口的例子是，例如无菌伤口、挫伤、切伤、撕裂伤、非穿透伤（即其中无皮肤破坏但损伤下面的结构的伤口）、开放性创伤、贯通伤、穿透伤、刺伤、脓毒性伤口、皮下创伤等。疮的例子有

褥疮、口疮、铬毒性溃疡、感冒疮、受压溃疡等。溃疡的例子是消化性溃疡、十二指肠溃疡、胃溃疡、痛风性溃疡、糖尿病性溃疡、高血压缺血性溃疡、淤积性溃疡、小腿溃疡 (静脉溃疡)、舌下溃疡、粘膜下溃疡、症状性溃疡、营养不良性溃疡、热带溃疡、软下疳（例如由淋病（包括尿道炎、宫颈内膜炎和直肠炎）引起的）。与伤口或疮有关的可以能根据本发明成功治疗的病症是烧伤、炭疽、破伤风、气性坏疽、猩红热（scalatina）、丹毒、寻常须疮、毛囊炎、传染性脓胞病或大疱性脓胞病等。术语“伤口”和“溃疡”以及“伤口”和“疮”的使用经常有一定的重叠，而且这些术语常常随机使用。因此，如上所述，在本文中，术语“伤口”包括术语“溃疡”、“损害”、“疮”和“梗死形成”，这些术语是不加区别地使用的，除非另外指出。

待根据本发明治疗的伤口种类还包括：i)一般的伤口，例如外科伤口、外伤、传染性伤口、缺血性伤口、烫伤伤口、化学伤口、大疱伤口；ii)特别针对口腔的伤口，例如拔牙后伤口、特别是与治疗囊肿和脓肿有关的牙髓伤口、细菌、病毒性或自免疫原性溃疡和损害、机械伤口、化学伤口、烫伤伤口、感染性伤口和苔癣样伤口；具体例子是疱疹溃疡、疱疹性口炎、急性坏死性牙疳和口灼伤综合征；和 iii)皮肤上的伤口，例如肿疡、烧伤（例如化学烧伤、烫伤）、损害（细菌性、病毒性、自免疫性）、咬伤和外科切口。其他的伤口分类方法是：i)归因于外科切口、轻微擦伤和轻微咬伤的小的组织损失，或 ii)严重的组织损失。后面的类别包括缺血性溃疡、受压溃疡、瘘、撕裂、严重咬伤、热烧伤和供区伤(在软组织和硬组织中)和梗死形成。

在本发明的其他方面，待预防和/或治疗的伤口选自无菌伤口、梗死形成、挫伤、切伤、撕裂伤、非穿透伤、开放性创伤、贯通伤、穿透伤、刺伤、脓毒性伤口和皮下创伤。

与本发明有关的其它重要伤口是如缺血性溃疡、受压溃疡、瘘、严重咬伤、热烧伤和供区伤的伤口。

在一个实施方案中，本文所述的化合物作为物理治疗/康复的辅药或作为同化剂用于伤口愈合。在另一个实施方案中，本文所述的化合物用于促进前交叉韧带（ACL）或内侧交叉韧带（MCL）损伤的愈合或加速 ACL 或 MCL 术后恢复。在另一个实施方案中，本文所述的化合物用于提高运动能力。在另一个实施方案中，本文所述的化合物用于治疗烧伤。在另一个实施方案中，

本文所述的化合物用于促进软骨再生。在另一个实施方案中，本文所述的化合物用于预防、治疗或逆转与长期的危重病、肺功能障碍、呼吸机依赖、衰老、AIDS、创伤、外科手术、充血性心力衰竭、心肌病、烧伤、癌症、COPD相关的分解代谢。在另一个实施方案中，本文所述的化合物用于预防或逆转由创伤引起的蛋白质分解代谢。在另一个实施方案中，本文所述的化合物用作：a) 在外科手术中使用的灼烙疗法（cauterization therapy）（激光或辐射）的辅药以促进伤口愈合，b) 冷冻疗法的辅药以促进伤口愈合，c) 化学疗法的辅药以预防副作用，例如脱发、性腺功能减退症、肌萎缩，骨质减少、骨质疏松症、少肌症、LDL、甘油三酯(TG)或总胆固醇增加、HDL 减少。在另一个实施方案中，本文所述的化合物用于慢性分解代谢状态（昏迷、消耗性病症、饥饿、进食障碍）；并发性骨折和肌肉损害；其中有明显的肌肉或骨消耗的危重病；和/或结缔组织疾病和病症。

缺血性溃疡和压迫溃疡是通常愈合得极慢的伤口，特别在这种情况下，改善而快速的愈合当然对病人很重要。而且，当愈合改善且发生得更快时，治疗罹患这种伤口的患者所涉及的费用显著减少。

供区伤的发生与例如硬组织从身体的一个部位移动至身体的另一个部位（例如移植）有关。由这种手术引起的伤口十分疼痛，因此，改善愈合十分有价值。

术语“皮肤”以非常广泛的意义使用，包括皮肤的表皮层，在皮肤或多或少地损伤的情况下，也包括皮肤的真皮层。除了角质层以外，皮肤的表皮层是外（上皮）层，而较深的皮肤结缔组织层称为真皮。

在一些实施方案中，烧伤与睾酮水平降低相关，而性腺功能减退症与伤口愈合延迟相关。在一个实施方案中，本发明的方法提供治疗罹患伤口或烧伤的个体。

在一些实施方案中，本发明提供用于促进前交叉韧带（ACL）或内侧交叉韧带（MCL）损伤愈合或加速 ACL 或 MCL 术后恢复的方法。

在一些实施方案中，本发明提供用于治疗个体的内分泌病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药、治疗胃肠系统的药、

治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，内分泌病症包括肢端肥大症、艾迪生病、肾上腺疾病、先天性肾上腺增生、雄激素不敏感综合征、先天甲状腺功能减退症、库欣综合征、尿崩症、糖尿病、1 型糖尿病、2 型糖尿病、糖尿病酮症酸中毒、空蝶鞍综合征、内分泌腺肿瘤、内分泌系统疾病、巨人症、性腺障碍、格雷夫斯病、两性同体、醛固酮增多症、高血糖高渗性非酮性昏迷、垂体功能亢进、高催乳素血症、甲状腺功能亢进症、性腺功能减退症、垂体功能减退症、甲状腺功能减退症、卡尔曼综合征、纳尔逊综合征、甲状旁腺疾病、垂体疾病、自身免疫性多内分泌腺病、青春期延迟、早熟青春期、肾性骨营养不良、甲状腺疾病、甲状腺激素抵抗综合征、甲状腺肿瘤、甲状腺结节、甲状腺炎、自身免疫性甲状腺炎、亚急性甲状腺炎或者 Wolfram 综合征。

在一个实施方案中，“性腺功能减退症”是由生殖腺功能性活动异常降低导致的或以其为特征的病症，并伴有生长和性发育延迟。

在一些实施方案中，本发明提供用于治疗个体的泌尿生殖器疾病和/或能育性、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包含给予个体组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗感染药、治疗肾脏的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，泌尿生殖器疾病和/或能育性疾病包括流产、自发性骨盆粘连、外阴阴道念珠菌病、产后抑郁、妊娠糖尿病、精神性性交困难、难产、子痫、子宫内膜异位症、死胎、胎儿生长迟缓、胎盘破裂过早、女性生殖器疾病、女性生殖器肿瘤、葡萄胎、妊娠剧吐、不孕、卵巢囊肿、卵巢扭转、盆腔炎性疾病、胎盘疾病、胎盘功能不全、多囊卵巢综合征、羊水过多、产后出血、妊娠并发症、异位妊娠、外阴瘙痒、产褥期疾病、产褥感染、输卵管炎、滋养层肿瘤、子宫颈功能不全、子宫内翻、子宫脱垂、阴道疾病、外阴疾病、外阴硬化性苔癣（vulvar lichen sclerosis）。

在一些实施方案中，本发明提供用于治疗个体的血液和/或淋巴疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。

在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，血液和/或淋巴疾病包括纤维蛋白原缺乏血症、贫血、再生障碍性贫血、溶血性贫血、先天非球形红细胞性贫血（congenital nonspherocytic anemia）、巨幼细胞贫血、恶性贫血、镰状细胞贫血、肾性贫血、血管淋巴样增生伴嗜酸细胞增多、抗凝血酶 III 缺乏、Bernard-Soulier 综合征、血液凝固障碍、血小板疾病、蓝色橡皮疱样痣综合征、切东二氏综合征、冷球蛋白血症、弥漫性血管内凝血、嗜酸粒细胞增多、Erdheim-Chester 病、胎儿幼红细胞增多症、伊万思综合征、因子 V 缺乏、因子 VII 缺乏、因子 X 缺乏、因子 XI 缺乏、因子 XII 缺乏、范科尼贫血、巨淋巴结增生、血液病、血红蛋白病、阵发性血红蛋白尿、血友病 A、血友病 B、新生儿出血病、组织细胞增多病、朗格汉斯细胞组织细胞增生症、非朗格汉斯细胞组织细胞增生症、乔布综合征、白血球减少症、淋巴结炎、淋巴管平滑肌增多症、淋巴水肿、高铁血红蛋白血症、骨髓增生异常综合征、骨髓纤维化、髓样化生、骨髓增殖性疾病、嗜中性白血球减少症、副蛋白血症、血小板存贮池缺如、真性红细胞增多症、蛋白质 C 缺乏、蛋白质 S 缺乏、紫癜、血小板减少性紫癜症、血栓性血小板减少、RH-同种免疫、结节病、结节病、球形红细胞增多症、脾破裂、地中海贫血、血小板无力症、血小板减少、Waldenstrom 巨球蛋白血症或血管性血友病。

在一些实施方案中，本发明提供用于治疗个体的先天性、遗传性或新生儿疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药物、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，先天性、遗传性或新生儿疾病包括艾卡迪综合征、羊膜带综合征、无脑畸形、Angelman 综合征、运动失调性毛细血管扩张症、Bannayan-Zonana 综合征、Barth 综合征、基底细胞痣综合征、贝-威二氏综

合征、布卢姆综合征、腮-耳-肾综合征、猫眼综合征、大脑性巨人症联合畸形综合征（cerebral gigantism-charge syndrome）、染色体 16 异常、染色体 18 异常、染色体 20 异常、染色体 22 异常、Costello 综合征、猫叫综合征、Currarino syndrome 综合征、囊性纤维化病、De Lange 综合征、10q 远侧三体性（distal trisomy 10q）、唐氏综合征、外胚层发育不良症、胎儿酒精综合征、胎儿疾病、胎儿-胎儿输血、脆 X 综合征、弗-谢二氏综合征、腹裂、先天性遗传性疾病、脐疝、前脑无裂畸形、色素失调症、伊维马克综合征、雅各布斯综合征、黄疸、克兰费尔特综合征、拉尔森综合征、劳-穆二氏综合征、无脑回、小头畸形、9p 单体性、指甲膝盖综合征、神经纤维瘤病、神经元蜡样质脂褐质沉积病、努南综合征、Ochoa 综合征(尿路面容综合征（urofacial syndrome），具有古怪面部表情的肾盂积水)、眼脑肾综合征、Pallister-Killian 综合征、帕-魏二氏综合征、Proteus 综合征、梨状腹综合征、Rett 综合征、罗比挠综合征、鲁-塔二氏综合征、脑裂、左右转位、史-伦-奥三氏综合征、Smith-Magenis 综合征、斯特季-韦伯二氏综合征、先天性梅毒、毛发低硫营养不良、三 X 女性、13 三体性(帕塔综合征)、9 三体性、特纳综合征、联体儿、乌谢尔综合征、瓦尔登布尔氏综合征、维尔纳综合征或 Wolf-Hirschhorn 综合征。

在一些实施方案中，本发明提供用于治疗个体的结缔组织疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药物、免疫调节剂、治疗皮肤病症的药、抗感染药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，结缔组织疾病包括强直性脊柱炎、Ehlers-Danlos 综合征、亨诺-许兰氏紫癜、川崎病、马方综合征、结节性多动脉炎、多肌炎、银屑病关节炎、反应性关节炎、类风湿性关节炎、硬皮病、干燥综合征、干眼病、斯蒂尔病、系统性红斑狼疮、塔卡亚萨病或韦格纳肉芽肿病。

在一些实施方案中，本发明提供用于治疗个体的代谢病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗糖尿病药、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的

药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，代谢病包括酸碱平衡失调、酸中毒、碱中毒、尿黑酸尿症、α-甘露糖苷贮积症、先天性氨基酸代谢障碍、淀粉样变、缺铁性贫血、抗坏血酸缺乏、维生素缺乏症、脚气病、生物素酰胺酶缺乏、碳水化合物缺乏糖蛋白综合征、毒碱病症（carnitine disorders）、胱氨酸贮积症、胱氨酸尿、脱水、法布里病、脂肪酸氧化障碍、岩藻糖苷贮积症、半乳糖血症、戈谢病、吉尔伯特病、葡糖磷酸脱氢酶缺乏、戊二酸血症、糖原贮积病、Hartnup 病、血色素沉着病、血铁质、肝豆状核变性、组氨酸血症、同型胱氨酸尿症、高胆红素血症、高钙血症、高胰岛素血症症、高钾血症、高脂血症、高草酸尿、维生素 A 过多症、低钙血症、低血糖症、低钾血症、低钠血症、低磷酸酯酶血症、胰岛素抵抗、碘缺乏、铁超负荷、慢性特发性黄疸、利氏病、莱-奈二氏综合征、亮氨酸代谢障碍、溶酶体贮积病、镁缺乏、枫糖尿病、Melas 综合征、门凯氏卷发综合征、代谢疾病、代谢综合征 X、先天性代谢缺陷、线粒体疾病、粘脂质累积病、粘脂质累积病、尼曼匹克病、肥胖症、鸟氨酸氨甲酰转移酶缺乏症、骨软化症、糙皮病、过氧化物酶体失调、苯丙酮尿、红血球生成性卟啉病、卟啉症、假性早衰、戈谢病、雷夫叙姆病、Reye 综合征、佝偻病、桑德霍夫病、饥饿、丹吉尔病、泰-萨克斯病、四氢生物蝶呤缺乏、三甲胺尿症(trimethylaminuria)、酪氨酸血症、尿素循环障碍、水电解质平衡失调、韦尼克脑病、维生素 A 缺乏病、维生素 B12 缺乏病、维生素 B 缺乏、沃尔曼病或 Zellweger 综合征。

在一些实施方案中，本发明提供用于治疗个体的环境因素诱发疾病（disorder of environmental origin）、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药物、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，环境因素诱发疾病包括耳气压伤、咬伤和蜇伤、脑震荡、烧伤、中心核综合征、颅脑损伤、电击伤、骨折、冻伤、

热应激障碍、晕动病、职业病、中毒、惊吓婴儿综合征、肩损伤、太空运动病、脊髓损伤、蜱性麻痹或伤口(贯通性和非贯通性) 。

在一些实施方案中，本发明提供用于治疗个体的行为机制病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和治疗心血管系统的药物、治疗中枢神经系统的药物、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一个实施方案中，行为机制病包括攻击、对死亡的态度、共同依赖、自伤行为、性行为或社会行为。

在一些实施方案中，本发明提供用于治疗个体精神障碍、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和治疗中枢神经系统的药物、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，精神障碍包括阿斯佩格综合征、注意力缺陷障碍伴多动、注意力缺陷障碍伴多动、双相型障碍、边缘型人格障碍、替身综合征、儿童行为障碍、战时神经症、循环性情感障碍、依赖性人格障碍、抑郁症、分离型精神障碍、心境恶劣障碍、进食障碍、纵火行为、疑病症、冲动控制障碍、克-列二氏综合征、精神障碍、儿童期诊断的精神障碍、多重人格障碍、米肖森综合征、芒氏综合征、代理明肖森综合征（Munchhausen by proxy）、自恋型人格障碍、发作性睡眠、强迫性障碍、性变态、恐怖症、精神病、不宁腿综合征、精神分裂症、季节性情感障碍、性欲和性表现障碍、心理性性功能障碍、睡眠障碍、躯体型障碍、创伤后应激障碍、物质相关性障碍、自杀行为或者拔毛狂。

在一个实施方案中，“抑郁”指涉及身体、情绪和思维的疾病，其影响人吃饭、睡觉的方式、自我感知和考虑事物的方式的想法。抑郁的体征和症状包括缺乏活动兴趣、食欲缺乏或进食过量、缺乏表情、空虚、感觉绝望、悲观、内疚或无助、社交退缩、疲劳、睡眠障碍、集中、记忆或作决定困难、躁动、易怒、头痛、消化障碍或慢性疼痛。

在一个实施方案中，“认知”指认识的过程，特别是保持清醒、认识、思维、学习和判断的过程。认知涉及心理学、语言学、计算机科学、神经科学、数学、习性学和哲学领域。在一个实施方案中，“情绪”指脾气或精神状态。

如本文所指的，变化指认知和/或情绪的任何积极或消极变化。

在一些实施方案中，本发明提供治疗个体的肝病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、治疗胃肠系统的药、抗感染药、治疗肝脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一个实施方案中，肝病包括肝癌、原发性胆汁性肝硬变、自身免疫性肝炎、慢性肝病、肝硬化、肝炎、病毒性肝炎(甲型肝炎、乙型肝炎、慢性乙型肝炎、丙型肝炎、慢性丙型肝炎、丁型肝炎、戊型肝炎、肝炎X)、肝功能衰竭、黄疸、新生儿黄疸、肝细胞瘤、肝癌、肝脓肿、酒精性肝病、血色素沉着病、肝豆状核变性病、门静脉高压、原发性硬化性胆管炎、结节病、绦虫、泡状棘球蚴病、片形吸虫病、血吸虫病、戈谢病、Zellweger综合征、酒精中毒、食物中毒、肺炎球菌性肺炎或者嗜盐弧菌。

在一些实施方案中，本发明提供用于治疗个体的肾疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗胃肠道系统的药、抗感染药、治疗肾脏的药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，肾病包括肢端肥大症、急性肾衰竭(ARF)(淀粉样变)、常染色体显性多囊肾病、肾结石、肾脏囊肿、常染色体隐性多囊肾病、慢性肾衰竭(CRF)、慢性肾病、科-勒二氏综合征、肺源性心脏病、冷球蛋白血症、糖尿病肾病、血脂异常、戈谢病、肾小球肾炎、肺出血肾炎综合征、溶血尿毒症综合征、肝炎、肾癌、肾结石、白血病、脂蛋白血症、狼疮、多发性骨髓瘤、肾炎、多动脉性肾囊肿（polyartekidney cysts）、链球菌感染后肾小球肾炎、肾小球肾炎、肾痛、先兆子痫、肾结核、肾盂肾炎、肾小管性酸中毒肾病、链球菌所导致的中毒性休克综合征、血栓栓塞、弓形体病、泌尿道感染、膀胱输尿管反流或者威廉斯综合征。

在一个实施方案中，所述肾疾病或病症是急性的，或者在另一个实施方案中是慢性的。在一个实施方案中，其中可以使用所述治疗方法的肾脏疾病或病症的临床适应症包括管型尿、测量的肾小球滤过率或其它肾功能指标。

在一个实施方案中，本发明的方法用于易患肾疾病或病症的个体。在一个实施方案中，关于个体的短语“易患肾疾病或病症”与短语“处于风险的个体”的同义，其包括处于患急性或慢性肾功能衰竭的风险，或如果合理地预计所述个体将罹患与功能性肾单位进行性损失相关的肾功能进行性损失，则所述个体处于需要肾替代疗法的风险。具体的个体是否处于风险是可以由相关医学或兽医学领域的普通技术人员按常规作出的决定。

在一个实施方案中，患有肾病的个体，特别是患有终末期肾脏疾病（ESRD）的男性个体罹患性腺功能减退症，其中一些患有伴发的中度至重度蛋白质能量营养不良（PEM），其造成更高的促红细胞生成素（EPO）需要量，更低的生活质量(QOL)分数和更高的死亡率。许多人具有与性腺功能减退症有关的其它症状，包括疲劳、缺乏食欲、肌无力等。在一些实施方案中，本发明的治疗方法用于治疗与性腺功能减退症有关的症状，所述性腺功能减退症在所述个体中由女性雄激素缺乏（ADIF）引起；由老年男性雄激素缺乏（ADAM）（包括疲劳、抑郁、性欲降低、勃起功能障碍、认知下降、情绪下降）引起；由雄激素不足（男性或女性）、雄激素缺乏（男性或女性）引起。

在一个实施方案中，糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平(>30 mg/天或 20 μg/min)的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（>300 mg/24 h 或 200 μg/min）。在 1 型糖尿病患者，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

高血压是肾脏病的另一种共病因素。在一些实施方案中，根据本发明治疗肾脏病可以包括用本发明的化合物和治疗高血压的药剂进行同步治疗。

在一些实施方案中，本发明提供用于治疗个体的消耗性疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠道系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的

药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，消耗性疾病包括肌损伤、卧床休养、固定、神经损伤、神经病、糖尿病神经病变、酒精性神经病、脊髓亚急性联合变性、糖尿病、类风湿性关节炎、运动神经元疾病、迪谢内肌营养不良、腕管综合征、慢性感染、结核病、艾迪生病、成人脊髓性肌萎缩（sma）、肢体肌萎缩、酒精性神经病、厌食、神经性厌食、与恶病质相关的厌食、与衰老相关的厌食、后纵隔肿瘤（back tumour）、皮肌炎、髋关节癌、包涵体肌炎、色素失调症、肋间神经痛、幼年型类风湿关节炎、累-卡-佩三氏病、肌萎缩、多灶性运动神经病变、肾病综合征、成骨不全、小儿麻痹症后期综合征、肋骨肿瘤、脊髓性肌萎缩、反射性交感神经营养不良综合征或泰-萨克斯病。

在本文中，消耗性病症或障碍定义为至少部分地以体重、器官质量或组织质量的异常的进行性损失为特征的病症或障碍。消耗性病症可以作为疾病例如癌症的结果而发生，或可归因于生理或代谢状态，例如废用性失调，所述废用性失调可以因长期卧床或当四肢被固定（例如在铸型中）时而发生，或因出现多个伤口（包括例如在糖尿病中出现的截肢、和其它病症）而发生，本领域的技术人员会理解这一点。消耗性病症也可以是年龄相关的。在消耗性病症过程中发生的体重减少的特征可以是总体重的减少或器官重量的减少，例如归因于组织蛋白减少的骨量或肌肉量的减少。

在一个实施方案中，术语“肌萎缩（muscle wasting）”或“肌萎缩（muscular wasting）”指肌肉量的进行性损失和/或肌肉的进行性衰减和退化，包括控制运动的骨骼肌或随意肌和控制心脏的心肌和平滑肌。在一个实施方案中，所述肌萎缩病症或障碍是慢性肌萎缩病症或障碍。“慢性肌萎缩”在本文中定义为肌肉量的慢性（即持续很长一段时间的）进行性损失和/或肌肉量的慢性进行性衰减和退化。

肌萎缩过程中发生的肌肉量损失可以是以由于肌肉蛋白分解代谢造成的肌肉蛋白分解或降解为特征。蛋白质分解代谢因为异常高速的蛋白质降解、异常低速的蛋白质合成或这两种的结合而发生。无论是由高度的蛋白质降解还是低度的蛋白质合成引起的肌肉蛋白分解代谢或消耗都会导致肌肉量的减少和肌萎缩。术语“分解代谢”具有本领域中普遍知晓的含义，特别是指能量燃烧形式的新陈代谢。

肌萎缩可以作为病状、疾病、病症或障碍（包括通过本发明的方法治疗的疾病，例如终末期肾功能衰竭）的结果而发生。

在一些实施方案中，本发明提供用于预防抑制素诱导的横纹肌溶解的方法。在一些实施方案中，本发明提供用于预防抑制素诱导的横纹肌溶解、器官衰竭或功能不全的方法。在一些实施方案中，本发明提供用于预防抑制素诱导的肾功能衰竭或肝功能衰竭或不全的方法。在一个实施方案中，所述方法包括向个体给药包含本发明的化合物和抑制素的组合物。

在一个实施方案中，所述消耗性疾病是个体的恶病质或非意愿体重减轻。在另一个实施方案中，本发明提供用于治疗、预防、抑制、减少或压制罹患肾脏病的个体的肌萎缩的方法。在另一个实施方案中，本发明提供用于治疗、预防、抑制、减少或压制罹患肾脏疾病或病症的个体的蛋白质分解代谢的方法。

恶病质是由疾病引起的或作为疾病副反应的虚弱和体重减少。由于疾病或损伤而长期住院或例如当肢体被固定时发生的废用性失调也能导致肌萎缩。研究显示，长期住院的罹患损伤、慢性病、烧伤、创伤或癌症的患者中，出现长期单侧肌萎缩和由此引起的体重减少。神经系统损伤，例如本文进一步叙述的脊髓损伤，也可能是致病因素。

在一些实施方案中，本发明提供用于治疗个体的消耗性疾病或病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在另一个实施方案中，所述消耗性疾病和病症尤其包括：a) 获得性免疫缺陷综合征（AIDS）消耗；b) 与卧床休息有关的消耗；c) 贪食症和/或与贪食症有关的消耗；d) 恶病质；e) 癌症恶病质；f) HIV 消耗；g) 由以下因素引起的减轻体重的恶病质和蛋白质损失：长期的危重病、肺功能障碍、呼吸机依赖、衰老、AIDS、创伤、充血性心脏衰竭、心肌病、烧伤、癌症、慢性阻塞性肺疾病（COPD）、进食障碍例如贪食病、神经性厌食、食欲缺乏、饥饿和/或抑郁。

在一些实施方案中，本发明提供用于治疗个体的无效状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述无效状态是小儿麻痹症后期综合征。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和免疫调节

剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠道系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。

在一些实施方案中，本发明用本发明的化合物提供辅助治疗。例如，在一个实施方案中，在疾病、障碍或病症的治疗（其中使用锻炼和限制饮食）中，给药本发明的化合物包括在这种治疗方案中。例如，在一个实施方案中，如本领域的技术人员将认识的，用本发明的化合物进行的辅助疗法或治疗，结合限制饮食和/或锻炼的，可能是用于治疗胰岛素抵抗、葡萄糖耐受不良、体重减轻、糖尿病、心血管疾病、代谢综合征、癌症、肌萎缩等的疗法。

在一些实施方案中，本发明提供用于治疗个体的性腺功能减退状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的性腺功能减退状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中，性腺功能减退症是由治疗引起的，所述治疗改变激素自女性和男性性腺的分泌。在一些实施方案中，性腺功能减退症可能是“原发性的”或“中枢性的”。在原发性性腺功能减退症症中，卵巢或睾丸本身不正常地发挥作用。在一些实施方案中，性腺功能减退症可能是由外科手术、辐射、遗传性病症和发育障碍、肝病和肾病、感染或某些自免疫疾病诱导的。在一些实施方案中，绝经是性腺功能减退症的形式。在一些实施方案中，绝经可能导致闭经、热潮红、阴道干燥或归因于女性雌激素水平下降的易激惹。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的骨质减少状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的骨质减少状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中，骨质减少是骨量的轻微减少。在一些实施方案中，骨质

减少是骨质疏松症的前兆。在一些实施方案中，骨质减少定义为比正常年青成人的骨密度低 1-2.5 个标准偏差（SD）的骨密度。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的少肌状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的少肌状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中少肌症是严重的肌肉量减少。在一个实施方案中，少肌症的定义是具有比低于正常年青成人的平均值 2 个标准偏差更低的瘦体重。在一些实施方案中，少肌症由以下原因引起：遗传因素、循环系统改变、毛细管:肌纤维比率降低、运动神经元改变、去神经支配、运动神经末梢板衰退、I 型纤维选择性神经移植术、造成肌肉损害的炎症应答、运动减少、营养不良、低膳食蛋白摄入量、维生素 D 缺乏、年龄相关的维生素 D 减少、氧化性应激、肌肉线粒体突变、特定类型肌纤维的改变、肌肉蛋白减少、致残疾病、卒中、阿尔茨海默氏病、帕金森病、骨质疏松症、动脉粥样硬化、糖尿病、高胰岛素血症、肾功能衰竭或性腺功能减退症。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含 SARM 化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的如上文所述的疾病和/或病症的组合、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的

药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

应该理解，如本文所述的本发明的任何方法都包括向个体给药本文所述的化合物或包含它的组合物，以治疗所指的疾病、障碍或病症。每一种本文所述的方法和/或其全部还可能包括给药本文所述的其它治疗剂，本领域的技术人员会理解这一点。

在一些实施方案中，本发明提供用于促进例如乳、精子或卵细胞的产生的方法。在一些实施方案中，本发明提供用于促进瘦肉或卵细胞的产生的方法。在一些实施方案中，本发明提供用于提高饲喂或配种牲畜的生产力的方法，例如增加精子计数、改善精子形态等。在一些实施方案中，本发明提供用于延长农场动物（例如产蛋母鸡、产奶奶牛等）的生产期和/或提高兽群健康（例如改善免疫清除、强壮动物）的方法。

在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素、营养添加剂、激素（每一种和/或全部均如本文所述）、或如本文所述的任何其它治疗剂、或它们的组合。

在另一个实施方案中，本发明提供用于治疗个体的以下疾病的方法：囊性纤维化病及由其引起的诱导性性腺功能减退状态、癫痫及由其引起的诱导性性腺功能减退状和/或代谢亢进状态、遗传性血管性水肿、红斑狼疮及由其引起的 BMD 下降、饮酒和抽烟诱导的骨质疏松症，所述方法包括向所述个体给药本文所述的 SARM。

在另一个实施方案中，本发明提供用于治疗个体的以下疾病的方法：小儿麻痹症和小儿麻痹后综合征及其它无效状态、抑制素诱导的横纹肌溶解症、抑制素诱导的肌无力、抑制素诱导的器官衰竭或功能不全，所述方法包括给药本文所述的化合物和任选适当的抑制素（本本领域的技术人员会理解这一点），和/或任何治疗剂。

在另一个实施方案中，本发明提供用于治疗阿片样物质诱导的雄激素缺乏（OPIAD）的方法，所述方法包括向个体给药本文所述的化合物和任选地

阿片剂、阿片样物质、麻醉药等、美沙酮、长效阿片剂/阿片样物质例如 Kadian、缓释吗啡（所有阿片剂/阿片样物质/麻醉药均获得 FDA 批准）、用于治疗海洛因成瘾的阿片剂/阿片样物质、用于治疗恶性肿瘤慢性疼痛的阿片剂/阿片样物质、用于治疗非恶性肿瘤的慢性疼痛综合征的阿片剂/阿片样物质。

在另一个实施方案中，本发明提供用于治疗神经系统疾病、障碍或病症的方法，所述方法包括向所述个体给药本文所述的化合物和任选的抗精神病药（例如佐替平、氟哌啶醇、氨磺必利、利培酮、其它多巴胺 D2 受体拮抗剂）、抗癫痫病药物（例如丙戊酸、卡马西平、奥卡西平（oxcarbamazepine）等）或它们的组合物。

在另一个实施方案中，本发明提供用于治疗激素依赖性疾病、障碍或病症的方法，所述方法包括向所述个体给药本文所述的化合物和任选地化疗剂和治疗（甲氨蝶呤、环磷酰胺、异环磷酰胺、阿霉素、多柔比星、糖皮质激素、环孢菌素、L-甲状腺素、SERM、抗炎药、氟维司群、GnRH 剂、ADT、中止激素替代疗法、颅脑照射、周边照射（peripheral irradiation）等；诱导高催乳素血症（prolactinemia）的药物治疗（通过 5HT2 受体作用的血清素能性的抗抑郁剂、选择性血清素再摄取抑制剂、单胺氧化酶抑制剂、三环抗抑郁剂、抗高血压药例如甲基多巴、利血平、可乐定和维拉帕米；抗多巴胺能的止吐药例如甲氧氯普胺，H2 受体拮抗剂例如西咪替丁和雷尼替丁，雌激素，苯丙胺，AR 部分拮抗剂（酮康唑、螺内酯、依普利酮）

在另一个实施方案中，如本文所述的本发明的化合物和组合物用于促进或加速手术操作后恢复。

在一个实施方案中，本发明提供本文所述的化合物用于减少个体的脂肪量的用途。在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合或者含有它们的组合物的这种使用方法。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合或者含有它们的组合物的以下用途：治疗腹部脂肪累积；治疗肥胖性少肌症；改善身体成分；减少体脂含

量；减少脂肪量；改善血脂谱（profile），增加肌肉量/肌肉强度/肌肉功能；增加骨量/BMD/骨强度/骨功能；减少体脂；先天性高胰岛素血症；库欣病（高皮质醇血症（hypercortisolemia））；个体的与代谢综合征相关的肥胖症或糖尿病。

在另一个实施方案中，所述个体患有激素失调、激素病症或激素疾病。在另一个实施方案中，所述个体处于绝经。

在一个实施方案中，本发明提供本文所述的化合物用于增加个体的瘦体重的用途。在另一个实施方案中，这种用途包括给药本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合。

在一个实施方案中，所述个体患有激素失调、激素病症或激素疾病。在另一个实施方案中，所述个体处于绝经。

实施例 15 显示，式(I)的化合物是合成代谢性的，但是其雄激素性最低，因此，这种化合物可以用于治疗过去雄激素是禁忌的患者群。无论睾酮是否存在，式(I)的化合物都显示促进肌肉生长，同时对前列腺施加抗增殖作用，因此，在一个实施方案中，本发明的方法用于恢复患有少肌症或恶病质的个体损失的肌肉量。

在一个实施方案中，本文所述的化合物改变个体的瘦素水平。在另一个实施方案中，本文所述的化合物降低瘦素的水平。在另一个实施方案中，本文所述的化合物增加个体的瘦素水平。已知瘦素对肥胖症小鼠的食欲、体重减轻有影响，因此其已与肥胖症有关。

在一个实施方案中，本文所述的化合物影响瘦素的循环水平，在另一个实施方案中，影响瘦素的组织水平。在一个实施方案中，术语“瘦素的水平”指瘦素的血清水平。如本文所指的，本发明的化合物对体外和体内的瘦素有影响。瘦素的水平可以用本领域的技术人员已知的方法来测定，例如通过可商购的 ELISA 试剂盒来测定。而且，可以通过本领域技术人员已知的任何方法在体外测定或体内测定中测定瘦素的水平。

由于瘦素与控制食欲、减轻体重、摄取食物和能量消耗有关，所以，调节和/或控制瘦素的水平是治疗、预防、抑制罹患肥胖症个体的肥胖症、降低其发病率的有用的治疗方法。调节瘦素的水平可以导致缺乏食欲、减少食物

摄取、增加瘦素个体的能量消耗，因此，可能有利于控制和治疗肥胖症。

在一个实施方案中，术语“肥胖症”定义为由脂肪在身体内过度累积导致体重增加超过骨骼的限制和身体的需要

在一个实施方案中，术语“肥胖症相关的代谢失调”指由肥胖症引起的、作为肥胖症的后果的、因肥胖症而加重的或继发于肥胖症的病症。这种病症的非限制性的例子是骨关节炎、II 型糖尿病、血压增加、卒中和心脏病。

胆固醇、甘油三脂和其它脂质通过脂蛋白在体液中运输，所述脂蛋白可以根据它们的密度划分为例如极低密度脂蛋白（VLDL）、中密度脂蛋白（IDL）、低密度脂蛋白（LDL）和高密度脂蛋白（HDL）。

已显示，LDL-胆固醇在血液中的高水平与动脉粥样硬化有关，动脉粥样硬化是部分地以脂质在动脉特别是冠状动脉的内壁中沉积为特征的进行性疾病。而且已经显示，也 LDL-胆固醇的高血液水平与冠心病有关。而且，HDL 胆固醇的血液水平与冠心病之间存在负相关。

血液中的总胆固醇水平（其为 HDL-胆固醇、LDL-胆固醇、VLDL-胆固醇和乳糜微粒-胆固醇的总和）不一定是冠心病和动脉粥样硬化风险的预兆。

但是，动脉粥样硬化和 LDL 胆固醇水平之间的关联比动脉粥样硬化和总血清胆固醇水平之间的类似关联高得多。

在一个实施方案中，本发明提供将本文所述的化合物用于改善个体的脂质谱和/或减少循环脂质水平的使用方法。在一些实施方案中，根据本发明的这一方面，所述个体罹患选自以下的一种或多种病症：动脉粥样硬化症及其相关疾病、过早衰老、阿尔茨海默氏病、卒中、中毒性肝炎、病毒性肝炎、周围血管功能不全、肾病和高血糖症，而且本发明用于给药本文所述的化合物或含有它的组合物，在一些实施方案中，所述化合物或组合物积极地影响所述个体的脂质谱，这是所述方法用于治疗所指的疾病、障碍和病症的一种手段。

在一个实施方案中，本发明提供治疗动脉硬化症及其相关疾病，例如心血管病症、脑血管障碍、周围血管病症、肠血管病症或它们的组合。

在一个实施方案中，心血管病症包括高血压（HTN）、冠脉疾病（CAD）或心肌灌注。在另一个实施方案中，本发明提供本文所述的 SARM 化合物用于促进主动脉平滑肌细胞增殖的使用方法。在另一个实施方案中，本发明提

供本文所述的化合物用于治疗动脉粥样硬化的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于降低血压的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于治疗心脏疾病和病症（包括心肌病、心功能不全例如心肌梗死、心脏肥大和充血性心力衰竭（cognitive heart failure））的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于保护心脏（包括在胰岛素抵抗中的保护心脏）的使用方；治疗 I 型和 II 型糖尿病、代谢综合征、X 综合征和/或高血压的使用方法。

在一个实施方案中，本发明提供用于治疗、预防个体的心血管和/或脑血管疾病、降低其死亡风险的方法，所述方法包括给药式(I)的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合、或者含有它们的药物组合物。在一个实施方案中，所述化合物以式(I) 的结构为特征。

在一个实施方案中，式 I 的化合物降低 LDL 和总胆固醇的水平。在另一个实施方案中，式(I)的化合物降低个体的 LDL 和总胆固醇的水平。

在另一个实施方案中，式 I 的化合物与升高 HDL 的药剂联合给药。在另一个实施方案中，式(I)的化合物与升高 HDL 的药剂联合给药。在另一个实施方案中，升高 HDL 的药剂包括烟酸。在另一个实施方案中，所述升高 HDL 的药剂包括贝特类，所述贝特类包括吉非贝齐（Lopid）、硫脲系吉非贝齐类似物和非诺贝特（TriCor）。在另一个实施方案中，升高 HDL 的药剂包括他汀类药物。在另一个实施方案中，升高 HDL 的药剂包括 1-羟基烷基-3-苯硫脲及其类似物。

在一个实施方案中，本发明提供用于降低个体的循环脂质水平的方法，所述方法包括给药式 I 的化合物或其药学上可接受的盐、水合物、*N*-氧化物或它们的任意组合、或者含有它们的组合物。在一个实施方案中，所述个体罹患动脉粥样硬化及其相关疾病、过早衰老、阿尔茨海默氏病、卒中、中毒性肝炎、病毒性肝炎、周围血管功能不全、肾病、高血糖或它们的任意组合。

在一个实施方案中，本发明提供用于治疗个体的动脉粥样硬化及其相关疾病（例如心血管病症、脑血管障碍、周围血管病症或肠血管病症）的方法，所述方法包括向所述个体给药式 I 的化合物或其药学上可接受的盐、水合物、*N*-氧化物或它们的任意组合、或者含有它们的组合物的步骤。所述方法还可

以包括同时、随后或在先给药已知可用于治疗心血管疾病、脑血管障碍、周围血管病症或肠血管病症的一种或多种药剂。

在一个实施方案中，本发明提供改善个体的灵活性和运动的方法，例如通过治疗所述个体的关节炎。

在另一个实施方案中，术语“关节炎”指主要发生在老年人中的非炎性退行性关节病，它以关节软骨变性、骨头及边缘肥大、滑膜改变等为特征。在另一个实施方案中，它还伴有疼痛和僵硬，特别是在长期活动之后。

在一个实施方案中，术语“糖尿病”指胰岛素的相对或绝对缺乏，导致不受控制的糖代谢。大多数患者在临床上可被划分为患胰岛素依赖型糖尿病（IDDM 或 I 型糖尿病）或非胰岛素依赖型糖尿病（NIDDM 或 II 型糖尿病）。

在其它实施方案中，术语“血压增加”或“高血压”指在超过 90/140 mmHg 的重复性高血压。慢性高血压可以造成眼底血管改变、心肌增厚、肾功能衰竭和脑损害。

在其它实施方案中，术语“卒中”指由于供血不足引起脑神经细胞损害，所述供血不足经常由血管破裂或血凝块造成。在其它实施方案中，术语“心脏病”指心脏正常功能和活动发生障碍，包括心力衰竭。

而且，最近显示，雄激素涉及多能间质细胞定型为肌源性谱系并阻止分化为成脂谱系（Singh 等人, Endocrinology, 2003，7 月 24 日）。因此，所述化合物可用于本文所述的阻止脂肪生成和/或改变干细胞分化的方法。

在另一个实施方案中，本发明涉及加速、增加或促进个体减轻体重的方法，所述方法包括向所述个体给药有效加速、增加或促进所述个体减轻体重的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及降低、压制、抑制或减少个体的食欲的方法，所述方法包括向所述个体给药有效降低、压制、抑制或减少所述个体的食欲的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及改变个体的身体成分的方法，所述方

法包括向所述个体给药有效改变所述个体的身体成分的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。在一个实施方案中，改变所述身体成分包括改变所述个体的瘦体重、去脂体重或它们的组合。

在另一个实施方案中，本发明涉及改变个体的瘦体重或去脂体重的方法，所述方法包括向所述个体给药有效改变所述个体的瘦体重或去肪体重的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及将个体的脂肪转化为瘦肌肉的方法，所述方法包括向所述个体给药有效将所述个体的脂肪转化为瘦肌肉的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及治疗个体的肥胖症相关的代谢失调的方法，所述方法包括向所述个体给药有效治疗所述个体的肥胖症相关的代谢失调的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及预防、压制、抑制或减轻个体的肥胖症相关的代谢失调的方法，所述方法包括向所述个体给药有效预防、压制、抑制或减轻个体的肥胖症相关的代谢失调的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体或它们的任意组合的步骤。

在一个实施方案中，所述肥胖症相关的代谢失调是高血压。在另一个实施方案中，所述病症是骨关节炎。在另一个实施方案中，所述病症是II型糖尿病。在另一个实施方案中，所述病症是血压增加。在另一个实施方案中，所述病症是卒中。在另一个实施方案中，所述病症是心脏病。

在另一个实施方案中，本发明涉及降低、压制、抑制或减少个体脂肪形

成的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及改变个体的干细胞分化的方法，所述方法包括向所述个体给药有效改变所述个体的干细胞分化的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在一个实施方案中，本文所述的化合物用于：a) 治疗、预防、压制、抑制或减轻肥胖症；b) 加速、增加或促进减轻体重；c) 降低、压制、抑制或减少食欲；d) 改变身体成分；e) 改变瘦体重或去脂体重；f) 将脂肪转化为瘦肌肉；g) 治疗、预防、压制、抑制或减轻肥胖症相关的代谢失调，例如高血压、骨关节炎、糖尿病、青春晚期糖尿病（MODY）、血压增加、卒中或心脏病；h) 降低、压制、抑制或减少脂肪形成；i) 改变干细胞分化；和/或 j) 改变瘦素水平。

在一个实施方案中，本文所述的化合物用于治疗或中止糖尿病的进展或治疗糖尿病症状。在另一个实施方案中，本文所述的化合物用于治疗与糖尿病相关的并发症。这些病症包括：高血压（HNT）、脑血管病、冠状动脉粥样硬化性心脏病、黄斑变性、糖尿病视网膜病（眼病）和失明、白内障一全身性炎症（以炎症指标例如红细胞沉降率或 C 反应蛋白的增加为特征）、出生缺陷、与妊娠有关的糖尿病、先兆子痫和妊娠高血压、肾病（肾功能不全、肾功能衰竭等）、神经疾病（糖尿病神经病变）、浅表和全身性真菌感染、充血性心力衰竭、痛风/高尿酸血症、肥胖症、高甘油三酯血症、高胆固醇血症、脂肪肝症（非酒精性脂肪性肝炎或 NASH）、以及糖尿病相关的皮肤病例如糖尿病脂性渐进环死（NLD）、糖尿病大水疱（糖尿病性大疱症）、发疹性黄瘤、Digital Sclerosis、播散性环状肉芽肿和黑棘皮病。

在一个实施方案中，本发明提供治疗、压制、抑制以下人类个体的疾病、或降低其发病率的方法：(a) I 型糖尿病；(b) II 型糖尿病；(c) 葡萄糖耐受不良；(d) 高胰岛素血症；(e) 胰岛素抵抗；(f) 肾病；(g) 糖尿病神经病变；(h) 糖尿病视网膜病；(i) 脂肪肝症；(j) MODY 和(k) 心血管疾病，所述方法包

括向所述个体给药式(I)的化合物的步骤。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与患糖尿病的个体相关的疾病或病症的应用或治疗。在一个实施方案中，寻求通过本发明的方法治疗的个体是患有 I 型糖尿病的个体。I 型糖尿病以胰腺 β 细胞的自身免疫破坏为特征。90%的个体在诊断时出现所述 β 细胞的免疫破坏标志，所述标志包括胰岛细胞（ICA）抗体、谷氨酸脱羧酶（GAD）抗体和胰岛素(IAA)抗体。尽管这种形式的糖尿病通常发生于儿童和青少年中，但是它可以发生于任何年龄。年轻个体的通常具有快速的 β 细胞破坏并与同时存在酮症酸中毒，而成年人经常保持充足的胰岛素分泌以防止酮症酸中毒达许多年。最终，所有 I 型糖尿患者需要胰岛素疗法以保持血糖量正常。

在一个实施方案中，本发明提供治疗 II 型糖尿病的方法。II 型糖尿病以胰岛素抵抗为特征，而且在该疾病发病的某个阶段以胰岛素分泌相对不足为特征。血浆胰岛素浓度（禁食和膳食刺激的）的绝对值通常增加，但是“相对于”胰岛素抵抗的严重性，血浆胰岛素浓度不足以维持正常的葡萄糖稳态。然而，随着时间推移，出现进行性 β 细胞衰竭，接着发生胰岛素绝对值不足。大多数患有 II 型糖尿病的个体表现出腹内性（内脏性）肥胖症、与胰岛素抵抗的存在密切相关的脂肪肝。所述患者的肝脏变成胰岛素抵抗性，糖原分解不受控制，结果是增加的、非生理性的葡萄糖被输送至血液中。肝脏产生的胆固醇和 VLDL 颗粒也不受控制。而且，这些个体通常存在高血压、血脂异常（高甘油三酯水平和低 HDL-胆固醇水平；餐后高脂血症）和 PAI-1 水平升高。这一连串异常被称为“胰岛素抵抗综合征”或“代谢综合征”或肥胖症相关的病症。由于这些异常，II 型糖尿病的患者罹患大血管并发症例如心肌梗死和卒中的风险增大。

在一个实施方案中，本发明提供治疗糖尿病肾病的方法。糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（>30 mg/天或 20 μg/min）的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（>300 mg/24 h 或 200 μg/min）。在 1 型糖尿病患者，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的

肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

在一个实施方案中，本发明提供治疗糖尿病神经病变的方法。糖尿病神经病变是由糖尿病引起的神经病症家族。糖尿病神经病变造成手、臂、足和腿麻木，有时造成它们疼痛和无力。糖尿病中的神经病学问题可能发生于每一个器官系统，包括消化道、心脏和生殖器。糖尿病神经病变划分为周围神经病变、自主神经病变、近端神经病变的和局灶性神经病变。周围神经病变造成趾、足、腿、手和臂的疼痛或感觉缺失。自主性神经病变造成消化、肠和膀胱功能、性反应和出汗的变化，也可影响服务心脏和控制血压的神经。近端神经病变造成股、髋或臀疼痛并导致腿无力。局灶性神经病变导致一条神经或一组神经的突然衰弱，造成肌无力或肌痛。身体内的任何神经都可能受影响。

在一个实施方案中，本发明提供治疗糖尿病视网膜病的方法。糖尿病对眼的影响称为糖尿病视网膜病。糖尿病患者更可能罹患眼疾，例如白内障和青光眼。糖尿病视网膜病对视觉的影响变化很广，取决于该疾病的阶段。糖尿病视网膜病的一些共有症状是视力模糊（这经常与血糖水平有关）、漂浮物（floaters）和闪烁（flashes）以及视力突然丧失。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有葡萄糖耐受不良的个体。葡萄糖耐受不良是糖尿病前期，其中，血糖高于正常水平，但没有高到确保诊断为糖尿病。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有高胰岛素血症的个体。高胰岛素血症是导致胰腺分泌过量胰岛素的潜在问题的征兆。高胰岛素血症的最普遍的原因是胰岛素抵抗，在这种病症中，你的身体对抗胰岛素的效应，而胰腺试图通过产生更多胰岛素来补偿。高胰岛素血症与 II 性糖尿病有关。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有胰岛素抵抗的个体。胰岛素抵抗是其中正常量的胰岛素不足以使脂肪细胞、肌细胞和肝细胞产生正常的胰岛素反应的病症。脂肪细胞中的胰岛素抵抗造成储存的甘油三酯水解，这提高血浆中游离脂肪酸的水平。肌肉中的胰岛素抵抗减少葡萄糖的摄入，而肝脏中的胰岛素抵抗减少葡萄糖储存，这两种效应帮助提

高血糖。归因于胰岛素抵抗的高水平的血浆胰岛素是葡萄糖经常导致代谢综合征和 II 型糖尿病。

糖尿病和肝肥胖症一般与游离脂肪酸（FFA）水平升高有关，游离脂肪酸促进靶组织中的脂质蓄积和胰岛素抵抗，即主要减弱胰岛素在骨骼肌和肝脏中的作用。胰岛素的突出作用是减少自肝脏的葡萄糖输出。FFA 刺激肝脏糖异生，只要糖异生与肝糖原分解降低平行进行（被称为"肝自身调节"的补偿过程），糖异生本身不会导致肝脏葡萄糖输出增加。FFA 刺激胰岛素分泌，而胰岛素通过抑制胰高血糖素（糖原分解的诱导物）的分泌部分地阻止糖原分解。然而，长期高水平的 FFA 导致肝脏胰岛素抵抗，并因此破坏肝自身调节，导致肝葡萄糖产生增加和罹患 II 型糖尿病。脂肪肝和肝脏胰岛素抵抗是高血糖和 II 型糖尿病的主要驱动力。

在一个实施方案中，本发明提供抑制（改善）脂肪肝的方法，所述方法肝中的胰岛素抵抗被抑制（改善），由此解决 II 型胰岛素的基本问题。

在另一个实施方案中，所述糖尿病是 I 型糖尿病。在另一个实施方案中，所述糖尿病是 II 型糖尿病。

在一个实施方案中，本发明提供治疗、压制、抑制人类个体的糖尿病、降低其发病率的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在另一个实施方案中，所述糖尿病是 I 型糖尿病。在另一个实施方案中，所述糖尿病是 II 型糖尿病。

在一个实施方案中，本发明提供治疗患有葡萄糖耐受不良的人类个体的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的高胰岛素血症的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的胰岛素抵抗的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病肾病的方法，所

述方法包括向所述个体给药式 I 的选择性雄激素受体调节剂化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病神经病变的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病视网膜病的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的脂肪肝症的方法，所述方法包括所述个体给药式 I 的选择性雄激素受体调节剂化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的血管疾病的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供用于 a) 治疗、预防、压制、抑制动脉粥样硬化，b) 治疗、预防、压制、抑制归因于脂肪沉积的肝损害的方法，所述方法包括向所述个体给药有效治疗、预防或抑制动脉粥样硬化和归因于脂肪沉积的肝损害的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本文所述的化合物用于：a) 治疗、预防、压制、抑制或减轻动脉粥样硬化；b) 治疗、预防、压制、抑制归因于脂肪沉积的肝损害。

在一个实施方案中，动脉粥样硬化指可能从损害动脉最内层开始的慢性复杂疾病。在另一个实施方案中，损害动脉壁的原因可能包括：a) 血液胆固醇水平提高；b) 高血压；c) 烟草烟雾；d) 糖尿病。在另一个实施方案中，吸烟者的这一病症是可治疗的，尽管烟草烟雾可能会使动脉粥样硬化严重恶化并加速其在冠状动脉、大动脉和腿部动脉中的发展。类似地，在另一个实施方案中，本发明的方法可以用于治疗具有早年心血管疾病家族史的个体（其患动脉粥样硬化的风险增加）。

在一个实施方案中，归因于脂肪沉积的肝损害指脂肪在肝细胞中累积形成脂肪肝，脂肪肝可能与肝脏的炎症有关或可能导致肝脏炎症。这可以导致肝的瘢痕形成和硬化。当结瘢痕形成变为广泛性时，其称为肝硬化。

在另一个实施方案中，脂肪在肝脏中蓄积成为肥胖症。在另一个实施方案中，脂肪肝也与糖尿病、高血甘油三酯和大量饮酒有关。在另一个实施方案中，脂肪肝可能伴随某些疾病例如结核病和营养不良、治疗肥胖症的肠分流术、体内维生素 A 过量或使用某些药物比如丙戊酸（商品名：Depakene/Depakote）和皮质类固醇（可的松、泼尼松）而发生。有时脂肪肝作为妊娠并发症发生。

在一个实施方案中，患有肾病的个体，特别是患有终末期肾脏疾病（ESRD）的男性个体罹患性腺功能减退症，其中一些患有伴发的中度至重度的蛋白质-能量营养不良（PEM），其造成更高的促红细胞生成素（EPO）需要量，更低的 QOL 分数和更高的死亡率。许多人具有与性腺功能减退症有关的其它症状，包括疲劳、缺乏食欲、肌无力等。在一些实施方案中，本发明的治疗方法用于治疗与由所述个体的肾脏疾病或病症引起的性腺功能减退症有关的症状。

在一个实施方案中，糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（>30 mg/天或 20 μg/min）的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（>300 mg/24 h 或 200 μg/min）。在 1 型糖尿病个体，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

高血压是肾脏病的另一种共病因素。在一些实施方案中，根据本发明治疗肾脏病可以包括用本发明的化合物和治疗高血压的药剂进行同步治疗。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症包括与衰老相关的病症。在一个实施方案中，本文所述的化合物用于：a) 年龄相关的功能下降（ARFD）；b) 逆转或预防 ARFD；c) 逆转或预防老年人 ARFD；d) 逆转或预防 ARFD 引发的少肌症或骨质减少；e) 男性更年期、男性更年期血管舒缩综合征；f) 男性更年期乳腺发育、肌肉强度

/功能；g) 骨强度/功能；h) 愤怒；i) 无力；j) 慢性疲劳综合征；k) 认知损害；和/或 l) 改善认知功能。

在一个实施方案中，本文所述的化合物用于治疗炎症和相关病症，例如：a) 预防、治疗或逆转关节炎；b) 预防、治疗或逆转关节炎性病症，例如贝切特氏病(自动免疫性血管炎)、滑囊炎、二羟焦磷酸钙晶体沉积症(或假性痛风) (CPPD)、腕管综合征、结缔组织病症、克罗恩病、埃-当二氏综合征(EDS)，纤维肌痛、痛风、感染性关节炎、炎症性肠病(IBD)、少年关节炎，系统性红斑狼疮(SLE)、莱姆病、马方综合征、肌炎、骨关节炎、结节性多动脉炎、风湿性多肌痛、银屑病、银屑病关节炎、雷诺现象、反射性交感神经营养不良综合征、莱特综合征、类风湿性关节炎、硬皮病、干燥综合征、肌腱炎或溃疡性结肠炎；c) 预防、治疗或逆转自身免疫性疾病。

在一个实施方案中，本文所述的化合物用于预防医源性作用，包括急性疲劳综合征（手术后）或雄激素剥夺治疗（ADT）诱导的副反应，例如肌肉量减少、肌肉强度降低、脆弱、性腺功能减退症、骨质疏松症、骨质减少、BMD 降低和/或骨量减少。

在一个实施方案中，所述化合物和/或组合物和/或它们的使用方法用于治疗人类个体，其中，在一个实施方案中，所述个体是男性，或在另一个实施方案中，所述个体是女性。

在一个实施方案中，本发明的方法包括给药作为唯一活性成分的本发明的化合物。然而，用于以下的方法也包含在本发明的范围内：糖尿病和相关病症、激素疗法、干眼病、肥胖症、治疗前列腺癌、延缓前列腺的进展、以及预防和/或治疗前列腺癌的复发、男性避孕；治疗骨质疏松症、治疗与 AIDF 相关的病症以及治疗和/或预防慢性肌萎缩，所述方法包括联合一种或多种治疗剂给药所述化合物。这些药剂包括但不局限于：LHRH 类似物、可逆的抗雄激素、抗雌激素药、抗肿瘤药、5-α 还原酶抑制剂、芳香酶抑制剂、孕激素、通过其它细胞核激素受体作用的药剂、选择性雌激素受体调节剂（SERM）、孕激素、雌激素、PDE5 抑制剂、阿扑吗啡、二碳磷酸盐化合物和一种或多种其它的 SARM。

因此，在一个实施方案中，本发明的方法包括联合糖尿病药物（例如曲格列酮、罗格列酮和吡格列酮）给药本发明的化合物。在另一个实施方案中，

本发明的方法包括联合 LHRH 类似物给药所述的化合物。在另一个实施方案中，本发明的方法包括联合可逆的抗雄激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合抗雌激素药给药所述的化合物。在另一个实施方案中，本发明的方法包括联合抗癌药给药所述的化合物。在另一个实施方案中，本发明的方法包括联合 5-α 还原酶抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合芳香酶抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合孕激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合通过其它细胞核激素受体作用的药剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合选择性雌激素受体调节剂（SERM）给药所述的化合物。在另一个实施方案中，本发明的方法包括联合孕酮给药所述的化合物。在另一个实施方案中，本发明的方法包括联合雌激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合 PDE5 抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合阿扑吗啡给药所述的化合物。在另一个实施方案中，本发明的方法包括联合二碳磷酸盐化合物给药所述的化合物。在另一个实施方案中，本发明的方法包括联合一种或多种其它 SARM 给药所述的化合物。在一些实施方案中，本发明的方法包括联合制剂，所述制剂包含所述的化合物和上文所述的药剂。在一些实施方案中，例如为了应对部分待治疗患者亚群的需要或单个患者的需要，所述联合制剂可以变化，所述不同的需要可能归因于具体疾病、所述疾病的严重性、年龄、性别或体重，这可以由本领域的技术人员容易地确定。在一些实施方案中，本发明的方法包括处理单个患者的需要的个性化用药方法。在一个实施方案中，不同的需要可归因于具体疾病、所述疾病的严重性、患者的整体医学状态或所述患者的年龄。在一些实施方案中，个性化用药是应用基因组数据以更好地定向医学干预的递送。在一些实施方案中，个性化用药方法用作发现和临床测试本发明的新产品的工具。在一个实施方案中，个性化用药包括应用临床上有用的诊断工具，所述工具可能帮助确定病人对具体疾病或病症的易感性。在一些实施方案中，个性化用药是综合性的方法，其在药物和诊断的发现和发展的所有阶段利用患者和健康个体的分子分析来指导决定；通过改善的预防、诊断、治疗和监控方法将这种临床实践的知识应用于更有效地提供准确而高质量的医疗保健。

在一些实施方案中，可以以在动物或人类的雌性升值周期中有效调节能育性的量给药式(I)的化合物，或者在一些实施方案中，以有效控制人类月经周期不规律或有效同步或抑制商品化动物（例如鱼、牛、绵羊、猪、山羊或鸡）、实验室动物（例如猿、黑猩猩、大鼠、小鼠或豚鼠）或家养动物（狗、猫、雪貂、兔或马）的生育期的量给药式(I)的化合物。在一些实施方案中，可以以有效减少月经的量给药式(I)的化合物，由此用于治疗或预防贫血和痛经。在一些实施方案中，可以以有效预防或治疗经前期综合征、子宫内膜异位症、平滑肌瘤（子宫肌瘤）和/或卵巢囊肿的量给药式(I)的化合物。而且，对于患有或以前患有盆腔炎性疾病的个体（其中可能已发生输卵管瘢痕形成），可以使用式(I)的化合物以减少可能发生输卵管妊娠的几率。

在一些实施方案中，可以以有效预防妊娠的量给药式(I)的化合物。在一些实施方案中，这种给药可以在排卵前或性交前、或者在排卵后或性交后。在一些实施方案中，这种给药抑制个体的胚胎植入，或在一些实施方案中抑制个体排卵。

在一些实施方案中，可以以有效诱导雌性宫颈成熟的量给药式(I)的化合物。所述宫颈成熟可以是阵痛和分娩后代的准备、或是刮宫术的准备。在另一个实施方案中，实施这种给药以诱导胚胎或胎儿从个体娩出。

应理解，任何本文所述的化合物的任何用途都可以用于治疗本文所述任何疾病、障碍或病症，而且代表本发明的实施方案。

以下所示的实施例是为了更全面地说明本发明的优选实施方案。但是，它们无论如何都不应该被解释为限制本发明的广泛范围。

## 实施例

### 实施例 1

[

### 化合物 XIII 的合成

2-取代丙烯酸（化合物 46）与 4-氰基-3-三氟甲基苯胺反应，然后进行环氧化。在碳酸钾存在下用对-CN-苯酚使环氧化物开环，产生化合物 XIII，如图 1B 中所示。

**实施例 2**

**化合物 V 的合成**

4-氰基-3-三氟甲基苯胺与丙烯-2-磺酰氯（51）反应，进行环氧化，然后在碳酸钾存在下用 p-CN-苯酚使环氧化物开环，产生化合物 V，如图 1C 中所示。

**实施例 3**

**化合物 XI 的合成**

用 p-CN-苯酚使环氧乙烷基甲基氨基甲酸叔丁酯（54）开环，得到化合物 55 ，然后用 TFA 脱保护，得到氨基醇 56。将化合物 56 引入与 4-氟-2-三氟甲基苄腈的亲电取代反应中，形成化合物 58。将 58 氧化成相应的羰基衍生物 59，将 59 用于进一步的加成反应，得到化合物 XI，其如图 1D 中所示。

**实施例 4**

**化合物 XXXV 的合成**

由起始化合物 3,6-二氧杂-双环[3.1.0]己烷（60）制备 4-亚甲基-四氢呋喃-3-醇（61），如图 1E 显示。该化合物用于与 p-CN-苯酚（50）进行 Mitsunobu 型反应，形成化合物 62。用 $OsO_4$ 进行二羟基化，然后在 TEMPO 基(2,2,6,6-四甲基哌啶哌啶基氧)的存在下用 $NaClO_4$ 进行氧化，形成酸 64。使用亚硫酰二氯和 4-氰基-3-三氟甲基苯胺由化合物 64 产生化合物 XXI，如图 1E 中所示。

**实施例 5**

**化合物 XXXVI 的合成**

如实施例 4 中所述制备化合物 62，然后进行环氧化，得到化合物 65，如图 1F 中所示。用 4-CN-3-三氟甲基苯胺使环氧化物开环，产生化合物 XXXVI，如图 1F 中所示。

**实施例 6**

**化合物 XLVI 的合成**

4-氰基-3-三氟甲基苯胺与衣康酸酐（66）反应，得到中间体 67。进一步环氧化并用对-CN-苯酚使环氧化物开环，产生化合物 XLVI，如图 1G 中所示。

**实施例 7**

**化合物 XLIII 的合成（图 2）**

通过肖登-包曼二氏反应使吡咯烷-2-羧酸（56）酰化，得到异丁烯酰基吡咯烷-2-羧酸（57），随后在 *N*-溴丁二酰亚胺的存在下，将其内酯化，得到溴内酯（58）。在回流条件下，用 24% HBr 溶液将所述溴内酯（58）水解 1 h，随后进行后处理并在乙酸乙酯-己烷混合物中重结晶，得到高收率的 3-溴-2-羟基-2-甲基丙酸（59）[59：白色固体（收率：85%）Mp. 108°C $[\alpha]_D^{25}$ = +10.5 (c=2.5,10 MeOH) NMR ($^1$H, 300MHz, DMSO): 1.35 (s, 3H, $CH_3$), 3.5 (s, 1H, CH), 3.6 (s, 1H, CH), 4.0 (br, 1H, OH) MS: 205 ($M + Na^+$) $C_4H_7BrO_3$ 已计算出: C, 26.25; H, 3.86 发现: C, 26.28; H, 3.75]。

然后，通过在氩气氛下冷却至 0℃，用三溴乙醛保护化合物 59 的羟基和羧基，在搅拌下滴加浓硫酸。2h 后溶液变暗；移去冰浴，反应混合物在室温下搅拌过夜。溶液用冰稀释并用乙酸乙酯萃取，无水硫酸钠干燥并浓缩，得到化合物 60，从乙酸乙酯-己烷中重结晶后，该化合物的外观为白色晶体。[60: 白色固体（收率：89%） Mp. 97°C NMR ($^1$H, 300MHz, $CDCl_3$): 1.8 (s, 3H, $CH_3$), 3.7 (s, 2H, $CH_2$), 5.8 (s, 1H, CH) $C_6H_6Br_4O_3$ 已计算出: C, 16.17; H, 1.36;发现: C, 16.08; H, 1.25]。

将化合物 60 溶解在 1:1 的 2-丙醇与 1M NaOH 的混合物中并在室温下搅拌。3h 后，当通过 TLC 检测不到原料时，加入 4'-氟苯硫酚，反应混合物搅拌过夜。然后，用浓 HCl 将反应混合物调节至 pH 1，用乙酸乙酯萃取并用无水硫酸钠干燥。浓缩有机层，得到油。在己烷-乙酸乙酯-乙酸混合物中对反应混合物进行快速柱层析，然后在乙酸乙酯-己烷中进行重结晶，得到无色针状晶体。通过用浓 HCl 酸化反应混合物使该化合物水解以除去保护基，得到图 2 中所示的手性羟酸（55）[55：白色固体（收率：65%） M.p. 54℃; $[\alpha]_D^{25}$ = +24.85 (c=1.0, MeOH) NMR ($^1$H, 300MHz, $CDCl_3$):1.5 (s, 3H,

$CH_3$), 3.2 (d, 1H, CH), 3.4 (d, H, CH), 7.0 (m, 2H, Ar, $J$ = 2.0 Hz, 8.9 Hz), 7.5 (m, 2H, Ar, $J$ = 2.0 Hz, 8.9 Hz) MS: 无母离子峰 $C_{10}H_{11}FO_3S$，已计算出：C, 52.16; H, 4.82; 发现: C, 52.05.59; H, 4.76]。

通过于 0℃在氯仿介质中加入硫光气和碳酸氢钠，然后在室温下搅拌过夜，将 4-硝基-3-三氟甲基苯胺转化为相应的异硫氰酸盐（66）。浓缩反应混合物，将其萃取至乙酸乙酯中，干燥，蒸发，通过使用已烷-乙酸乙酯混合物的快速柱层析进行纯化，得到外观为黄色固体的 66。在搅拌下加入羟酸 55 和 4-硝基-3-三氟甲基苯基异硫氰酸盐（66）、三氟乙酸银乙腈溶液和三乙胺，反应混合物加热至回流，保持 1h。通过过滤除去硫化银，减压蒸去溶剂，所得剩余物用水洗涤，萃取至乙酸乙酯中，干燥、过滤并浓缩。通过使用已烷-乙酸乙酯混合物的快速柱层析进行分离，所期望的产物呈现为黄色油。鉴定该化合物是噁唑烷二酮（65），如图 2 中所示。[65: 黄色油(收率：52% )$[\alpha]_D^{25}$ = +39.7 (c=2.5,10 甲醇) NMR ($^1$H, 500MHz, DMSO): 1.8 (s, 3H, $CH_3$), 3.2 (s, 1H, 20 CH), 3.3 (s, 1H, CH), 6.9 (m, 2H, Ar, $J$ = 2.0 Hz, 8.9 Hz ), 7.2 (m, 2H, Ar, $J$ = 2.0 Hz, 8.9 Hz), 7.9 (m, 1H, Ar, $J$ = 2.1 Hz, 9.0Hz), 8.0 (m, 1H, Ar, $J$ = 0.5Hz, 2.1 Hz) 8.1 (m, 1H, Ar, $J$ = 0.5Hz, 9.0Hz) NMR ($^{13}$C, 500MHz, CDCl3): 22.8, 43.4, 86.7, 117.0, 117.3, 124.4, 124.5, 124.6, 125.0, 126.8, 129.3, 134.2, 134.3, 135.3, 164.9, 172.8 MS: 无母离子峰 $C_{10}H_{11}FO_3S$，已计算出：C, 48.65; H, 2.72; N, 6.30 发现: C, 48.59; H, 2.70; N, 6.31]。

该产物（65）在 π 受体/供体(R,R)-Whelk-O1 手性柱上的 HPLC 分析显示比率为 70:30 两个峰，对应两个对映异构体，对映异构体过量值为 40%。噁唑烷二酮形成的发生必定经过羟基从亚胺碳上亲核置换硫化银及随后的协同环重排，这可由中间结构（67a）和（67b）得到证实；与 Shibuya 等人建立的机制相同的机制。本文考虑，在上述分析型手性柱中获得的对映异构体的良好分离情况可以扩展至相应的制备柱，以便获得所述对映异构体的定量收率，由此用激子偶联振动圆二色性（exciton coupled vibrational circular dichroism）测定它们的绝对构型，并用以高斯经验计算法辅助测定红外光谱。本文还考虑，杂环体系的氧原子可以用氨基代换以得到对映性的比卡鲁胺的乙内酰脲类似物，然后所述类似物会为与受体的氢键合相互

作用提供额外的位点。

**实施例 8**

**化合物 XLVIII 的合成（图 3）**

通过重氮化由 4-氰基-3-三氟甲基苯胺制备 4-溴-2-三氟甲基苄腈（74）。使 4-溴-2-三氟甲基苄腈（74）与 BuLi 反应生成 Li 的衍生物（75）。使 3-溴苄腈与 BuLi 反应生成 Li 的衍生物（77）。用(2-溴乙氧基）-叔丁基二甲基硅烷（78）将 Li 衍生物（77）烷基化，得到衍生物（79），79 用 MeMgI 转化为苯乙酮（80）。随后，脱保护并与对-CN-苯酚发生 Mitsunobu 反应，形成苯乙酮（82）。加入 Li 衍生物（75），然后脱水，得到化合物 XLVIII，如图 3 中所示。

**实施例 9**

**化合物 XLIX 的合成（图 4）**

将 4-(2-羟基乙基)-吡啶-2-腈（83）用叔丁基二甲基硅烷保护，并用 MeMgI 将其转化为相应的苯乙酮（85），然后脱保护，制备醚（87）。加入 Li 衍生物（75），然后脱水，得到化合物 XLIX，如图 4 中所示。

**实施例 10**

**化合物 L 的合成（图 6）**

通过 4-氯甲氧基苄腈（97）由对-CN-苯酚（50）制备正膦（98），在维蒂希反应中 98 与 3-乙酰基苯甲醛（99）生成衍生物（100）。随后，加入如实施例 8 中所述的 Li 衍生物（75），然后脱水，得到化合物 L，如图 6 中所示。

**实施例 11**

**化合物 LI 的合成（图 7）**

用叔丁基二甲基硅烷保护 3-羟甲基苄腈（101），得到化合物（102），随后用 MeMgI 得到相应的苯乙酮（85）。除去保护基，进一步与对-CN-苯酚反应以得到（105）。向（105）中加入 Li 衍生物（75）（如实施例 8 中所

制备），然后脱水，得到化合物 LI，如图 7 中所示。

**实施例 12**

**化合物 LII 的合成（图 5）**

用叔丁基二甲基硅烷保护 5-溴-2-羟基苄腈（88），得到化合物（89）。化合物（89）与 BuLi 反应，得到 Li 衍生物（90），其进一步由(2-溴乙氧基)-叔丁基二甲基硅烷烷基化，得到（91）。化合物（91）与 MeMgI 反应成相应的苯乙酮（92），然后脱保护并选择性地保护酚基，得到衍生物（94）。衍生物（94）与对-CN-苯酚反应，得到化合物（95），然后加入 Li 衍生物（75）并脱水（如实施例 8 中所述），得到化合物（96）。随后脱保护，得到化合物 LII，如图 5 中所示。

**实施例 13**

**化合物 XXIV 的一般合成（图 1I）**

根据图 1I 制备 4-(4-芳基磺酰-2,5-二甲基哌嗪-1-基)-2-三氟甲基苄腈。于 DMSO-水混合物中在碳酸钾存在下，用 2,5-二甲基哌嗪亲核取代 4-氟-2-三氟甲基苄腈中的氟原子。在三乙胺存在下，通过与芳基磺酰氯的反应制备相应的芳基磺酰衍生物。

**实施例 14**

**雄激素受体（AR）与 SARM 的结合以及 AR-SARM 晶体结构**

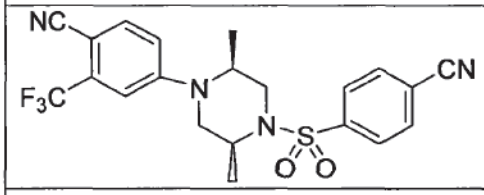
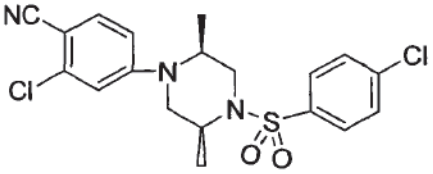
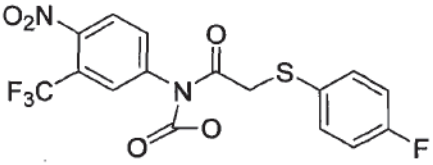
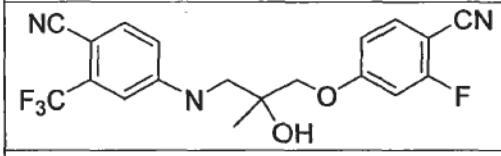
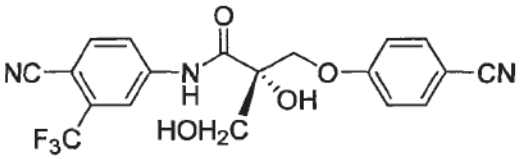
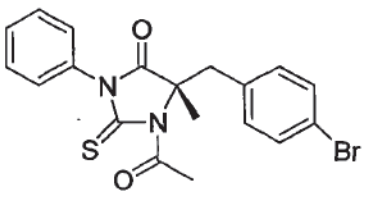
**方法**

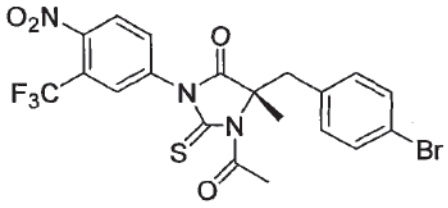
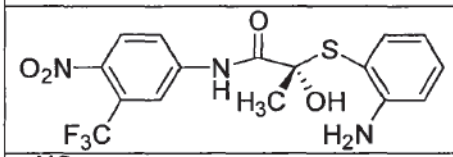
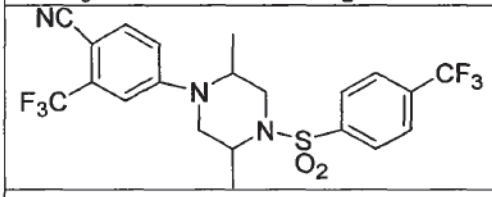
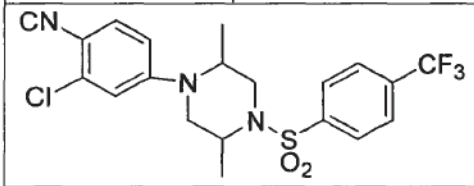
亲合力测定

由斯普拉-道来(氏)大鼠的腹部前列腺得到细胞溶胶 AR。切除前列腺并立即浸没在冰冷的匀浆缓冲液中（10 mM Tris、1.5 m MEDTA 二钠、0.25 M 蔗糖、10 mM 钼酸钠和 1 mM PMSF）。用剪刀将前列腺切碎，匀浆并离心（Model L8-M，Beckman Instruments Inc）。收集上清液（细胞溶胶）并储存在-80℃下直到使用。在存在或不存在浓度增加的感兴趣的化合物（$10^{-1}$ nM-$10^{4}$ nM）的情况下，于 4℃下用饱和浓度的 $^{3}$H-MIB (1 nM)和 1 μM 的曲安奈德培养等份（50 μL）的 AR 细胞溶质 18 h。

通过向培养液中加入 1000 nM MIB，测定 $^{3}$H-MIB 的非特异性结合。使用羟基磷灰石分离结合的和游离的放射性配体并测定结合的 $^{3}$H-MIB 的浓度。使用非线性回归测定 $IC_{50}$，即抑制 50% $^{3}$H-MIB 的特异性结合的供试化合物的浓度。

测定本发明的化合物的亲合力并显示在下表中：

| 化合物 | 抑制常数（nM） |
|---|---|
|  | 633.5 |
|  | 528.9 nM |
|  | 195.81 nM |
|  | 412.24 nM |
|  | 396.8 nM |
|  | 微摩尔范围 |

| | |
|---|---|
|  | 微摩尔范围 |
|  | 70.7 nM |
|  | 2785 nM |
|  | 2632 nM |

共转染测定

使 CV-1 细胞（绿猴肾细胞）在补充了 10% FBS、2mM 谷氨酰胺和 1% 链霉素和青霉素的达尔伯克氏改良伊格尔氏培养基（DMEM）上生长到在 T175 组织培养烧瓶中融合。无血清 DMEM 中，将细胞用 3 μg CMVhAR 表达载体、30 μg 雄激素依赖型萤光素酶报道基因构建体(pMMTV-luc)和 30 μg β-半乳糖苷酶表达构建体（pSV-β-半乳糖苷酶；Promega, 5 Madison, WI）经 30 mLPlus 试剂（Invitrogen）和 40 mL LipofectAMINE（Invitrogen）转染。4 小时后，将培养基换成补充 0.2 % FBS 和 2 mM 谷氨酰胺的 DMEM。12 小时后，将细胞转移至 24 孔组织培养板，再过 6 小时后，用 0.1 nM-1000 nM 的药物或不加药物（对照）处理。另外 24 小时后，细胞用冷 PBS 洗涤两次，通过用 100 ML 的被动性溶胞解缓冲液（Promega）培养 30 分钟后收集细胞。

将等份（50 mL）溶胞产物加到不透明的 96 孔板，在自动注入 50 mL 萤光素酶底物（Promega）后，用 MicroLumatPlus LB96V 发光计（Berthold Technologies, Oak Ridge, TN）使用 WinGlow 软件包监测萤光素酶的活性。另将等份（50 mL）的溶胞产物和 50 mL β-半乳糖苷酶测定缓冲液一起加到

透明的96孔板。在37℃下培养2小时后，在Dynex MRX读板器上于420 nm测定吸收值。使萤光素酶活性与 β-半乳糖苷酶活性标准化，以便计算细胞数量和/或转染率损失的差异。

克隆、表达和纯化

由全长 AR 表达构建体（pCMVhAR）通过用含有侧翼限制酶切位点的引物进行 PCR 扩增获得 AR-LBD（663-919），然后将其插入到 pGEX6P-1 质粒载体（Amersham）中。通过用 30μM IPTG 诱导，所述 AR LBD 于 15℃下在大肠杆菌 BL21 DE3 中表达 16 小时，为谷胱甘肽-S-转移酶（GST）融合蛋白。在含有 150 mM NaCl、50 mM Tris pH 8.0、5 mM EDTA、10% 甘油、1 mg/mL 溶菌酶、10 U/mLDNA 酶 I、10 mM $MgCl_2$、10 mM DTT、0.5% CHAPS、100 μM 配体和 100 μM PMSF 的缓冲液中，通过三次冻融循环，将细胞溶解。由超速离心得到的上清液与谷胱甘肽琼脂糖凝胶（Amersham）在 4℃下培养 1 h，并用 150 mM NaCl、50 mM Tris pH 8.0、5 mM EDTA、10%甘油、10 mM ATP、10 DM 配体、0.1% *n*-辛基-β-葡糖苷和 1 mM DTT 洗涤。

于 4℃下在含有 150 mM NaCl、50 mM Tris pH 7.0、10%甘油、0.1% *n*-辛基-β-葡糖苷、1 mM DTT 和 5 U/mg 蛋白质 PreScission 蛋白酶（Amersham）的缓冲液中过夜切割 GST-LBD 融合蛋白以从谷胱甘肽琼脂糖凝胶中释放 AR LBD。上清液在 10 mM pH 7.2 的羟乙基哌嗪乙磺酸、10%甘油、10 μM 配体、0.1% *n*-辛基-β-葡糖苷、1 mM DTT 中稀释 3 倍，然后装载至 HP SP 阳离子交换柱（Amersham）上。在相同的稀释缓冲液中用 50 mM-500 mM 的 NaCl 梯度洗脱蛋白。在 Millipore 10 kD 截留浓缩器中将缓冲液换成含有 150 mM $Li_2SO_4$, 50 mM pH 7.2 的羟乙基哌嗪乙磺酸、10%甘油、100 μM 配体、0.1% *n*-辛基-β-葡糖苷和 10 mM DTT 的缓冲液，将蛋白质浓缩至大于 4 mg/mL。

结晶、收集数据和结构测定

在一至两天内，利用悬滴蒸发扩散法于 0.1 M pH 7.5 羟乙基哌嗪乙磺酸和 0.5 M-0.8 M 的柠檬酸钠中形成 AR LBD 晶体。在液氮中快速冷冻之前，将 AR LBD 晶体转移至由 0.1 M pH 7.5 的羟乙基哌嗪乙磺酸、0.7 M 柠檬酸钠和 20%乙二醇组成的溶液中。使用 Rigaku RU300 旋转阳极发生器

和 R-轴 IV++成像板（Rigaku）收集衍射数据，并用 Crystal Clear 软件进行处理（Molecular Structure Corporation）。AR LBD-DHT 复合物（PDB 编码 1I37）用作使用 Crystallography & NMR System（CNS）进行精制的起始结构。在第一轮精制后，电子密度图使配体准确拟合（fitting）。使用程序 O 加入模型构建物和水分子，使用刚性体、扭转角模拟重结晶法和 CNS 的单个温度因子模块进行更多轮的精制。

SARM 的 X 射线研究

将显示 AR 结合低于 100 nM 的 SARM 在萤光素酶测定中进一步分析，以确定它们是否具有 AR 功能性激动剂活性。随后，使具有最高活性的 SARM 与 AR 受体共结晶并进行 X 射线分析。

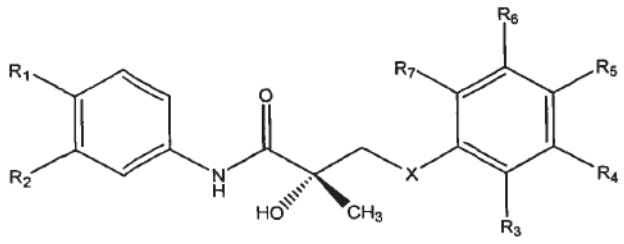
**实施例 15**

**SARM 的功能活性**

表 1 描述了所示醚连接化合物（比卡鲁胺类似物）的结构和亲合性。所有化合物都使用手性合成方法合成，包括使用 D-脯氨酸作为手性助剂，如美国专利 6,995,284 中所公开地，该专利通过引用结合于此。使用元素分析和波谱数据，即 $^{1}H$ NMR、$^{13}C$ NMR、MS 和 IRE 确定合成的化合物的结构。

在本发明的一些方面，这些化合物的设计充分理解被鉴定为涉及比卡鲁胺类似物的 AR 亲合力的结构元素，例如：(i) 缺电子的芳香性 A 环，(ii) 在手性中心的 *R*-构型，和(iii) 在 B 环的对位的亲电子基团。重要的是要注意，在这类分子中，当用醚键代替硫醚或磺酰基连接时，活性化合物的手性指示从*(R)*变为*(S)*。除了这些对高 AR 结合亲合力所需的结构特征外，B 环取代和连接基 X 的性质是比卡鲁胺类似物的功能活性的关键性决定因素。

表 1：

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| 编号 | R1 | R2 | X | R3 | R4 | R5 | R6 | R7 | $K_i$ (nM) |
|---|---|---|---|---|---|---|---|---|---|
| 比卡鲁胺 | CN | $CF_3$ | $SO_2$ | H | H | F | H | H | 11±2 |
| *R*-20 | $NO_2$ | $CF_3$ | $SO_2$ | H | H | COCH3 | H | H | 9.3±0.8 |
| S-1 | $NO_2$ | $CF_3$ | O | H | H | F | H | H | 6.1±0.19 |
| S-2 | $NO_2$ | $CF_3$ | O | H | H | COCH3 | H | H | 36.6±2.3 |
| S-3 | $NO_2$ | $CF_3$ | O | H | H | $COCH_2CH_3$ | H | H | 6.1±0.14 |
| S-4 | $NO_2$ | $CF_3$ | O | H | H | NHCOCH3 | H | H | 4.0±0.70 |
| S-5 | $NO_2$ | $CF_3$ | O | H | H | $CH_3$ | H | H | 34.8±3.5 |
| S-6 | $NO_2$ | $CF_3$ | O | H | H | OCH3 | H | H | 13.7±0.68 |
| S-7 | $NO_2$ | $CF_3$ | O | H | H | $NHCO_2C(CH_3)3$ | H | H | 336.0±71.1 |
| S-9 | $NO_2$ | $CF_3$ | O | H | H | H | H | H | 4.6±0.26 |
| S-10 | $NO_2$ | $CF_3$ | O | F | H | F | H | H | 3.4±0.34 |
| S-11 | $NO_2$ | $CF_3$ | O | H | F | F | H | H | 3.4±0.56 |
| S-12 | $NO_2$ | $CF_3$ | O | F | H | F | H | H | 3.2±0.30 |
| S-13 | $NO_2$ | $CF_3$ | O | CH3 | H | F | H | H | 6.0±0.70 |
| S-14 | $NO_2$ | $CF_3$ | O | H | Cl | F | H | H | 10.3±2.0 |
| S-15 | $NO_2$ | $CF_3$ | O | H | F | Cl | H | H | 4.9±0.3 |
| S-16 | $NO_2$ | $CF_3$ | O | H | Cl | Cl | H | H | 1.0±0.088 |
| S-17 | $NO_2$ | $CF_3$ | O | F | F | F | H | H | 11.3±1.1 |
| S-18 | $NO_2$ | $CF_3$ | O | F | H | F | H | F | 10.3±2.0 |
| S-19 | $NO_2$ | $CF_3$ | O | F | F | H | F | H | 9.1±0.6 |
| S-20 | $NO_2$ | $CF_3$ | O | F | F | F | F | F | 1.4±0.34 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| S-21 | $NO_2$ | $CF_3$ | O | H | H | Cl | H | H | 8.6±1.2 |
| S-22 | $NO_2$ | $CF_3$ | O | H | H | Br | H | H | 12.6±1.8 |
| S-23 | $NO_2$ | $CF_3$ | O | H | H | I | H | H | 22.6±1.6 |
| S-24 | $NO_2$ | $CF_3$ | O | H | H | $NHCSNH_2$ | H | H | 10.2±1.4 |
| S-25 | $NO_2$ | $CF_3$ | O | H | H | $NHCSNHCH_3$ | H | H | 271.2±37.2 |
| S-26 | CN | I | O | H | H | F | H | H | 3.3±0.10 |
| S-27 | CN | $CF_3$ | O | H | H | Cl | H | H | 3.4±0.08 |
| S-28 | CN | $CF_3$ | O | H | H | $NHCOCH_3$ | H | H | 12.7±0.02 |
| S-29 | CN | Cl | O | H | H | F | H | H | 4.5±0.11 |
| S-30 | CN | $CF_3$ | O | H | H | F | H | H | 3.3±0.08 |
| S-31 | F | $CF_3$ | O | H | H | F | H | H | 32.6±0.10 |
| S-32 | Cl | $CF_3$ | O | H | H | F | H | H | 14.5±0.18 |
| S-33 | I | $CF_3$ | O | H | H | F | H | H | 15.6±0.19 |
| S-34 | Br | $CF_3$ | O | H | H | Cl | H | H | 52.0±0.13 |
| S-35 | Br | $CF_3$ | O | H | H | Br | H | H | 25.9±0.04 |
| S-36 | H | $CF_3$ | O | H | H | F | H | H | 62.0±0.05 |

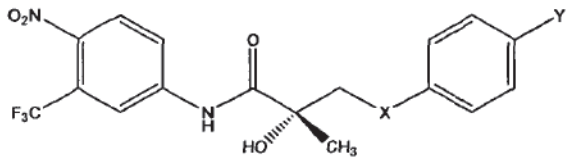
对 AR 介导的转录激活的体外研究（图 8）显示，将 X 连接由砜变为氧或将 B 环对位取代由氟变为乙酰胺基都将纯粹的 AR 拮抗剂转化为激动剂，例如在化合物 S-5 和 R-20 中。在体内试验中，先导化合物 S-1 和 S-4 在体内用作 AR 激动剂并显示出组织选择性（图 9A-9B)。S-1 和 S-4 在前列腺中都是部分激动剂，但是在肛提肌、骨和垂体中是完全激动剂，这些是对理想的选择性雄激素受体调节剂提出的特征。

S-4 的口服生物利用度和安全性已经被证实（数据未显示），确证了这些化合物可能有效治疗雄激素缺乏性疾病或病症的观点。先前已经证明，S-1 和 S-4 不是 5α-还原酶的底物。本文考虑，这些配体的组织选择性是因

为它们在前列腺中的激动剂活性没有完全被 5α-还原酶放大，5α-还原酶是在前列腺中而不是肌肉中表达的、将睾酮转化为 DHT 的酶。

表2显示最大疗效百分数对表1的各种化合物的X-和Y-位置的依赖性。如实施例 13 中所述，使用大鼠腹部细胞溶胶作为 AR 源，利用竞争性结合测定来测定完整 AR 的亲合力。如实施例 13 中所述，使用共转染测定，检测完整 AR 的体外功能活性。在 10 nM 配体下分析疗力（即转录激活），将活性表示为对 1 nM 双氢睾酮（DHT）观察到的最大转录激活的百分数。

**表 2**




| ID | X | Y | 亲合力 (nM) | 疗效 (%最大) |
|---|---|---|---|---|
| S-1 | O | F | 6.11 ± 0.19 | 43.40 ± 2.60 |
| X-2 | S | F | 11 ± 2 | 77.4 ± 5.6 |
| X-3 | $SO_2$ | F | 28 ± 10 | 18.8 ± 9.3 |
| X-4 | NH | F | 7.96 ± 0.43 | 21.33 ± 2.22 |
| X-5 | $CH_2$ | F | 9 ± 0.2 | 28.9 ± 2.4 |
| S-4 | O | $NH(CO)CH_3$ | 3.98 ± 0.70 | 92.92 ± 7.00 |
| S-23 | O | I | 23 ± 1.6 | 47.2 ± 1.8 |

**实施例 16**

非类固醇配体结合的结构表征

对一系列 4"-氟苯基-2-羟基-2-甲基-*N*-(4'-硝基-3'-三氟甲基苯基)丙酰苯胺化合物进行构象分析，这些化合物仅 X 位置的杂原子不同。该分析检

测了 X 位置取代基对溶液中化合物构象的影响以开发构象化合物。将配体溶液（DMSO-$d_6$）NMR 构象与它们的来自新近解析的 *R*-比卡鲁胺-W74L-LBD 晶体结构（本文中称为比卡鲁胺-W741L；C. E. Bohl, W. Gao, D. D. Miller, C. E. Bell, J. T. Dalton. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc Natl Acad Sci U S A* **2005**, *102(17)*, 6201-6. ）的结合构象作比较。已经预料在连接部位中的分子内氢的键合（NH-OH），这在溶液构象中观察到了。然而，对于一些被分析的化合物，这种分子内 NH 氢键供予在 OH 和 X 位置间共享。NH-X 氢键导致所述配体在溶液中的总体形状获得意想不到的弯曲，这种弯曲与在 AR 的同源建模过程中得到的假设性的结合构象明显不同。过去，对丙酰苯胺没有六元 5 环状 NH-X 氢键合构象的假设。激动剂 S-4(X=O,Y=N-乙酰基)和 X-2(X=S,Y=F)和部分激动剂 S-23(X=O,Y=I)和 S-1(X=O,Y=F)最清楚地显示出这种溶液中苯环的 NH 至-X 加-OH 构象（图 10），但是，对于该系列的拮抗剂 X-3(X=$SO_2$, Y=F)和 X-4(X=NH, Y=F)和 X-5(X=$CH_2$ ,Y= F)没有观察到这种构象。这表明，所述配体采取这种构象的能力可能对 AR 激活很重要，这一点通过与非类固醇配体的构象的比较得到确证，所述非类固醇配体的构象是在随后解析的 *R*-比卡鲁胺-W741L-LBD（AR 突变体，其中比卡鲁胺用作激动剂）的 X 射线晶体结构中观察到的。

表 3 提供表 1 所中所鉴定的各种化合物的溶液中分子内氢键分析的结果。如表 3 中使用的，氢键的定义是<3.1Å 的原子间距离，该距离是在 SYBYL 6.8 中使用分析->>距离命令测得的。

溶液构象使用 NOESY 谱测定。NH-OH 指连接部位酰胺的质子和连接部位羟基的氧之间的原子间距离，NH-X 指连接部位酰胺的质子和连接部位 X 位置的原子之间的原子间距离。S-1 在体外用作部分激动剂，S-4 和 X-2 在体外是激动剂，X-3、X-4 和 X-5 在体外是拮抗剂。

**表 3：**

| ID | NH-OH | NH-X |
|---|---|---|
| S-1 | 2.4 | 2.3 |
| S-4 | 2.7 | 1.9 |

| | | |
|---|---|---|
| X-2 | 2.1 | 3.0 |
| X-3 | 2.0 | 3.6 |
| X-4 | 2.3 | 4.4 |
| X-5 | 2.0 | 3.9 |

构建 AR 的位点特异性突变体，检测 DHT 和三种非类固醇配体即羟基氟他胺（HF）、比卡鲁胺和 S-4 刺激 AR 介导的转录的能力（图 11）。在该突变体中，比卡鲁胺表现为激动剂并刺激 AR 介导的转录激活，表明结合比卡鲁胺的 W741L 突变体 AR-LBD 采取类似于用结合激动剂的野生型 AR 观察到的构象的活性构象。考虑到纯化结合拮抗剂的野生型 LBD 的困难，结合比卡鲁胺的 W741L 突变体和结合羟基氟他胺的 T877A 突变体的激动剂构象证明是有用的。本文考虑，这些突变体复合物会采取更紧凑的构象，这样会促进在 LBD 的纯化和结晶过程中伴侣蛋白质的解离，并为我们提供对非类固醇 AR 配体结合机制的首次了解。

使用类似于首先解析与类固醇配体结合的 AR-LBD 晶体结构的科学家所述的方法，将结合 R1881 和 DHT、DHT-5 的野生型 LBD 和结合比卡鲁胺的 W741L LBD 纯化并结晶。而且，使用亲合力更高的比卡鲁胺 *R*-异构体。在大肠杆菌中，GST-LBD 与配体共同表达。在亲和层析和裂解融合蛋白后，LBD 的高 pI（等电点）使杂质蛋白和伴侣蛋白质通过中性 pH 阳离子交换色谱除去。

这两种复合物均采取与结合类固醇的 LBD 非常类似的整体构象（图 12A）。如由溶液构象的 NMR 研究所预示的，比卡鲁胺在磺酰基氧和胺类质子之间形成分子内氢键（图 12B），这与计算机预测的模型（图 10）不同，指示这是不同于醚连接类似物的构象，并表明对配体溶液构象的 NMR 研究可能用于预测与 LBD 结合时的配体构象。这种结象说明，这些突变为非类固醇配体提供更多的空间以嵌入（fit into）LBD，并形成由野生型 DHT 复合物观察到的激动剂构象。

大多数 LBD 残基在野生型 DHT 复合物中的位置类似于非类固醇复合物，尽管配体结构的变化程度惊人（图 13A）。羟基氟他胺（HF）和 *R*-比卡鲁胺具有类似的 A 环和酰胺键结构，这使类固醇平面完全重叠（图 13B）。

在 R752 和 A 环的硝基/氰基之间观察到氢键，这模拟了 DHT 中的 3-酮基，而且在 L704 和 N705 和羟基之间也观察到氢键，这模拟了 DHT 中的 17β-OH。然而，与 DHT 不同的是，在非类固醇配体和 T877 侧链之间没有观察到氢键。

在 R-比卡鲁胺的砜连接基和 B 环区域也观察到残基的位置有很大区别（图 13B），该区域折叠离开类固醇平面并指向口袋（pocket）的顶部，可能占用 W741 吲哚环(在突变体中不存在)的空间。在 T877A-HF 和 WT-DHT 复合物中，W741 吲哚环的位置也区别很大。在 DHT 复合物中，Trp741 侧链与配体接触，而在 T877A-HF 复合物中，该吲哚环距离结合口袋(binding pocket）更远。M745 由 DHT 的 19-甲基置换似乎能解释这些区别。在图 13B 中也看到，与野生型 DHT 和 T877A-HF 相比，*R*-比卡鲁胺磺酰基造成螺旋 12 残基 M895 的置换。然而，该 M895 侧链被容纳在 T877A-HF 复合物的 W741 吲哚环的位置中。在野生型 LBD 中，W741 和 M895 侧链都可能与比卡鲁胺具有不利的阻止激动剂构象形成的相互作用。另一方面，R-比卡鲁胺的 B 环对位上的氟在 AR 的亲水区域结合，所述区域也提供形成氢键的机会。AR 的这一区域位于螺旋 4 和 5 之间的扭转处并与 H874 咪唑十分接近。在该位置被乙酰胺基 S-4、异硫氰酸盐、氰基或硝基取代的化合物证明对 AR 具有改善的亲合力，表明在该区域它们可能形成有利的氢键。

**实施例 17**

**结合激动剂和拮抗剂的 AR LBD 的结构特征**

HSP 的解离是由激动剂诱导的 AR LBD 构象变化引起的初始过程之一。在哺乳动物细胞中，HSP 复合物主要包含 HSP90、HSP70、p60 和 p23。HSP90 直接与受体结合成为同型二聚体，而其它蛋白质主要通过 HSP90 与该复合物结合。AR LBD 中的 HSP90 结合位点还没有被很好地表征。包括环 3-4、H4 和 H5 的残基 720-774 正好形成大部分的 AF2 疏水性凹槽（图 14A-14B），它们被鉴定为可能负责使用截短的结合 HSP90 的区域。

重要地，本文考虑，异常的曝露于溶剂的 HSP90 的 α-螺旋与细胞核受体家族的 H12 非常类似，并可能置换这些受体上的 H12 以促进配体结合。

这个观点尤其可能与 AR 有关，因为 AR 的功能与其它细胞核受体相比似乎有重要的不同。放射标记的 AR 的 IP 和蔗糖梯度离心分析显示，激动剂 R1881（而不是拮抗剂羟基氟他胺和比卡鲁胺）诱导 HSP90 解离，这说明伴侣蛋白质复合物的存在而不是 H12 的 MAEII 模体阻止接近 AF2 区。因此，HSP90 的解离似乎直接与 AR 配体的活性有关。

虽然羟基氟他胺用作野生型 AR 的拮抗剂，但是它对 T877A AR 突变体起激动剂作用。其对突变的 AR 的激动剂活性直接与 HSP90 的解离有关。这与 ER 完全不同，其中 ER 激动剂和拮抗剂都启动 HSP 的解离。与 ER 的情况相比，HSP90 的解离对 AR LBD 似乎是能影响受体的构象的更关键的因素。这说明 AR 拮抗剂活性可能涉及另一种机制。

不同 AR 复合物的限制性蛋白水解分析表明，AR 的配体诱导的激活需要 LBD 的两次连续的构象变化。AR 激动剂，即 T、DHT 和 R1881，稳定了 AR 的 29-KD 片段对抗限制性胰蛋白酶消化，而抗雄激素，即醋酸环丙孕酮、羟基氟他胺、尼鲁米特和比卡鲁胺稳定 35-KD 片段。29-KDa 和 35-KDa 片段都含有完整的 LBD（氨基酸 671-919），35-KDa 片段延伸进入铰链区（氨基酸 621-671）。35-KDa 片段也参与激动剂结合的初始步骤，但是在长时间的消化作用下其不稳定。

这种时间依赖性构象变化被钼酸盐的加入而延迟，这说明 HSP 的解离可能导致铰链区暴露于胰蛋白酶消化。因此，已经提出，激动剂结合启动 AR 的第一次构象变化，这触发 HSP 的解离，然后开始第二次构象变化。然而，尽管拮抗剂能启动第一次构象变化，但是它不能促进 HSP 的解离，这稳定了 LBD 和铰链区并保护铰链区不受进一步的胰蛋白酶消化。

**实施例 18**

对 SARM 进行基于结构的药物设计（SBDD）的全新方法

在基于激动剂与 AR 的结合构象来设计激动剂方面，与拮抗剂比卡鲁胺结合的 AR 突变体 W741L（bicW741L）使我们洞悉本文提供的化合物的结合模式。这也为区分激动剂和拮抗剂的结合模式特征提供了原理。最近解析的结合激动剂 S-1 的野生型 AR（S1-野生型）的晶体结构确证了在 W741L 突变体中观察到的结合模式。在 1.8 Å 的清晰度下，这些结构都被

解析，而且这些结构证明了新型的结合模式，该模式根本上不同于在共晶结构出现之前提出的、由同源模型所表明的模式。

与上述共晶相反，同源模型沿所对接的（docked）类固醇的 α-面具有独特的未被占据的空腔，所述空穴大到足够能容纳丙酰苯胺的 B 环。

确认全新 SBDD 模型

通过Spearman相关系数分析对这些AR结构模型进行的经验分析提供了每一种模型预测配体亲合力的等级次序的能力的统计学手段。当使用基于分子对接的方法例如全新设计或虚拟筛选以评价该模型是否能用于按优先次序确定应该沿着哪些经计算机模拟（*in silico*）的指导进行时，这种等级顺序统计量是适当的。将为比较分子场分析（CoMFA）模型而编辑的 AR 配体数据库用于以下 AR 模型的 Spearman 分析：CoMFA、结合 S-1 的野生型晶体（简称为 S1-野生型），结合比卡鲁胺的 W741L 晶体（简称为比卡鲁胺 c-W741L）和同源模型。CoMFA (C. E. Bohl, C. Chang, M. L. Mohler, J. Chen, D. D. Miller, P. W. Swaan, J. T. Dalton. A ligand-based approach to identify quantitative structure-activity relationships for the androgen receptor. J Med Chem 2004, 47(15), 3765-76.)、S1-野生型(C. E. Bohl, D. D. Miller, J. Chen, C. E. Bell, J. T. Dalton. Structural basis for accommodation of nonsteroidal ligands in the androgen receptor. J Biol Chem 2005, 280(45), 37747-54.)、比卡鲁胺-W741L (C. E. Bohl, W. Gao, D. D. Miller, C. E. Bell, J. T. Dalton. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. Proc Natl Acad Sci U S A 2005, 102(17), 6201-6.)和 G1 同源模型((C. A. Marhefka, B. M. Moore, 2nd, T. C. Bishop, L. Kirkovsky, A. Mukherjee, J. T. Dalton, D. D. Miller. Homology modeling using multiple molecular dynamics simulations and docking studies of the human androgen receptor ligand binding domain bound to testosterone and nonsteroidal ligands.*J Med Chem* **2001**, *44(11)*, 1729-40.)的 $R_s$ 值分别为 0.93、0.55、0.29 和-0.28，这说明，S1-野生型模型显著的预测值和比卡鲁胺-W741L 模型有限的预测值表明与以前的基于结构的药物设计模型相比有进步。因此，可以预测这些晶体结构能改善确定由计算机模拟的指导的优先次序的能力，由此促进药物设计。

**实施例 19**

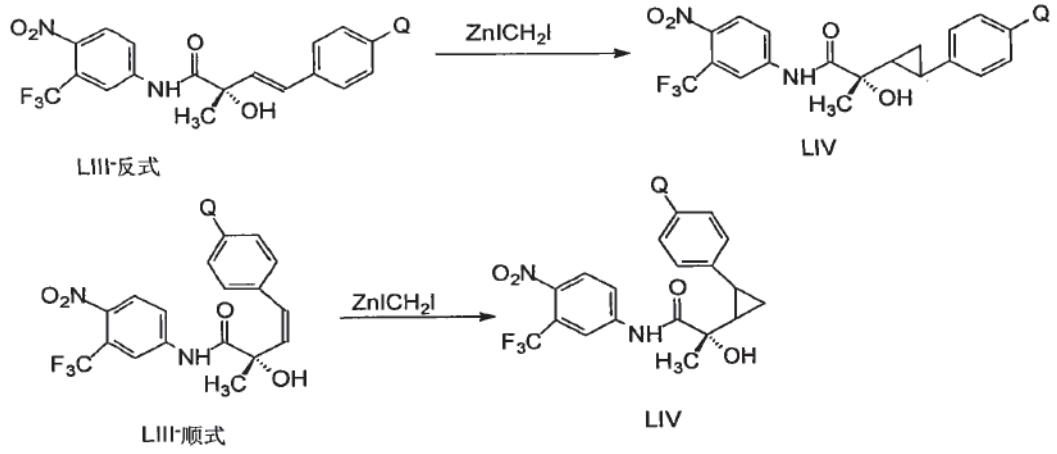
**AR 配体结合的计算预测的确认**

对实施例 16 中的扭应变参数和氢键相互作用的检验显示，化合物 XVII 的芳基丙酰胺衍生化合物采取类似于化合物 XLII 的构象。羟基 α 以这样的方式定位到羰基，它参与和受体的天冬酰胺 705 的氢键相互作用。该氨基酸与亮氨酸 704 的主链氧形成弱的氢键。所做的计算预测与结合测定得出的结果一致。然而，为了令人信服地建立上述相互作用和分子采取的构象，建立了合适的分子模型，该模型没有自由羟基和酰胺质子，而且最重要的是，该模型在构象上局限于类似于化合物 XLII 的结构。因此，酰胺氮和羟基氧通过羰基官能团连结，这形成如化合物 XXXIX 中所描绘的噁唑烷二酮衍生物结构。实施芳基丙酰胺衍生的化合物的合成和这些噁唑烷二酮衍生物的立体选择性合成。

**实施例 20**

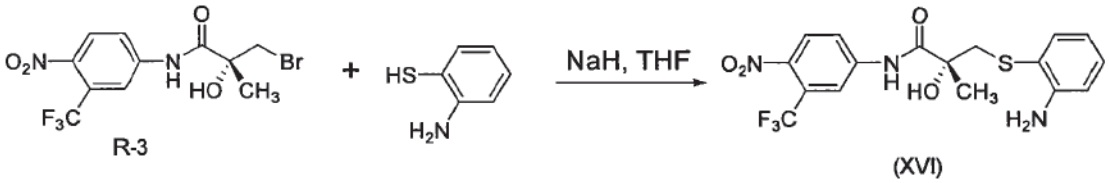
**化合物 LIV 的合成**

通过化合物 LIII 合成化合物 LIV，所考虑的第一组化合物是通过西蒙斯-史密斯反应合成的环丙烷系列，如以下路线所示。




**实施例 21**

**化合物 XVI 的合成**




根据上述路线合成化合物 XVI。根据 US 06995284 合成 R-3，该专利通过引用结合于此。得到 XVI，为黄色油：计算出的质量 415.08, [M-H] 414.0; $^1$H NMR ($CDCl_3$) 9.13 (bs, 1H, NH), 7.96 (d, J = 9.0 Hz, 2H, ArH), 7.88 (dd, J = 9.0, 2.1 Hz, 1H, ArH), 7.43 (dd, J = 7.6, 1.5 Hz, 1H, ArH), 7.11 (m, 1H, ArH), 6.72 (m, 2H, ArH), 4.15 (bs, 3H, OH & NH2), 3.59 (d, J = 14.1 Hz, 1H, CH2), 3.02 (d, J = 14.1 Hz, 1H, CH2), 1.56 (s, 3H, CH3)。

**实施例 22**

**化合物 XL 的合成**

如图 1J 中所描绘地合成化合物 XL。向乙醇中的 L-丙氨酸钠盐中加入异硫氰酸苯酯，温热 30 分钟。蒸去溶剂，并向油状剩余物中加入浓 HCl。收集形成的白色固体，在水中洗涤，得到化合物 2。加入乙酸酐，得到化合物 3，在六甲基二硅氮烷钾盐的存在下加入 1-溴-4-溴甲基苯，得到化合物 XL。

化合物 2 的 $^1$H NMR ($CDCl_3$)：7.65, 7.63, 7.61, 7.38, 7.35, 7.25, 4.40, 1.62

化合物 3 的 $^1$H NMR ($CDCl_3$)：7.59, 7.57, 7.56, 7.39, 7.33, 4.92, 2.90, 1.74

化合物 XL 的 $^1$H NMR ($CDCl_3$)：7.53, 7.52, 7.51, 7.50, 7.49, 7.40, 7.39, 7.37, 7.34, 4,38, 1.67, 1.66；化合物 XL 的熔点：99℃。

**实施例 23**

**化合物 XLI 的合成**

如图 1K 中所描绘地合成化合物 XLI。向乙醇中的 L-丙氨酸钠盐中加入 4-异硫氰基-1-硝基-2-三氟甲基苯，温热 30 分钟。蒸去溶剂并向油状剩余物中加入浓 HCl。收集形成的白色固体，在水中洗涤，得到化合物 2。加入乙酸酐，得到化合物 3，在六甲基二硅氮烷钾的存在下加入 1-溴-4-溴甲基苯，得到化合物 XLI。

化合物 3 的 $^1$H NMR ($CDCl_3$)：10.80, 8.35, 8.18, 7.99, 4.49, 1.43。

化合物 XLI 的 $^1$H NMR ($CDCl_3$)：7.97, 7.47, 7.43, 7.42, 7.19, 7.15, 6.97,

6.92, 3.93, 3.15, 2.88, 1.98。

虽然本文已经说明和描述了本发明的某些特征，但是本领域的普通技术人员现在会得出许多修改、替换、改变和等同形式。因此，应该理解，所附的权利要求书意在覆盖所有落在本发明的真正精神范围内的这种修改和变化。

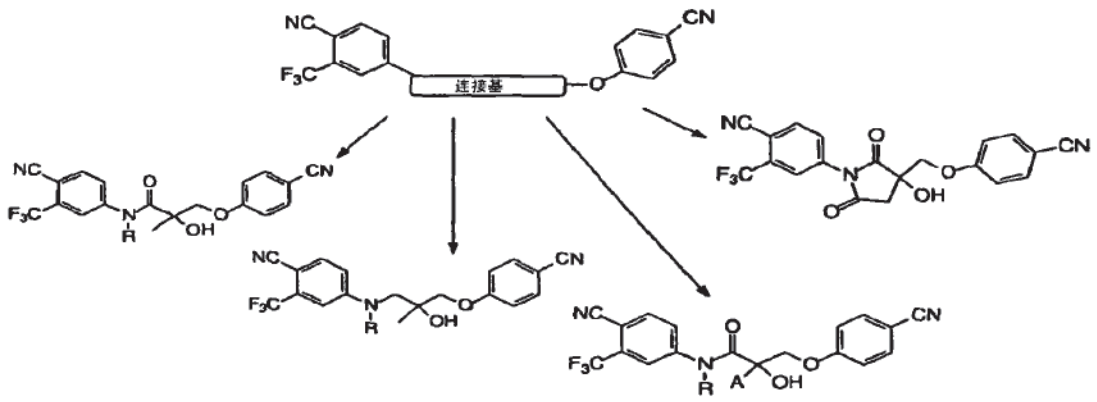

NC
CN
F3C
连接基
O
N
R
OH
A

图1A

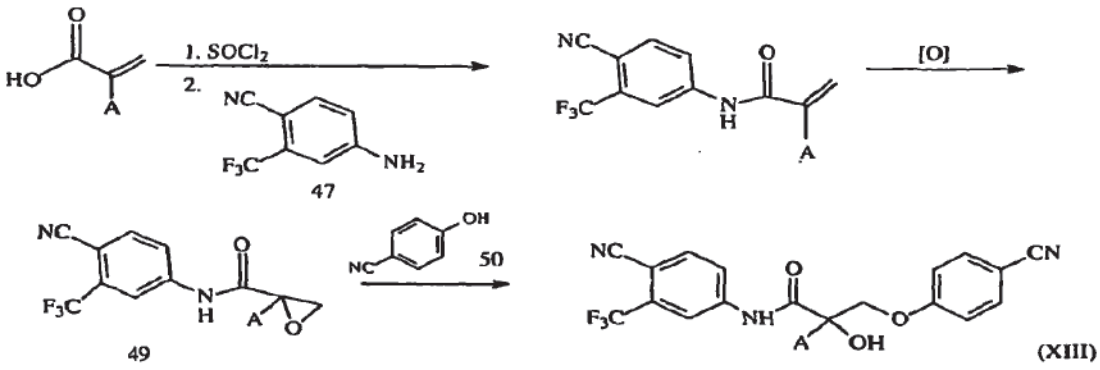

HO
O
A
1. SOCl2
2.
NC
F3C
NH2
47
[O]
NH
49
50
OH
CN
(XIII)

图1B

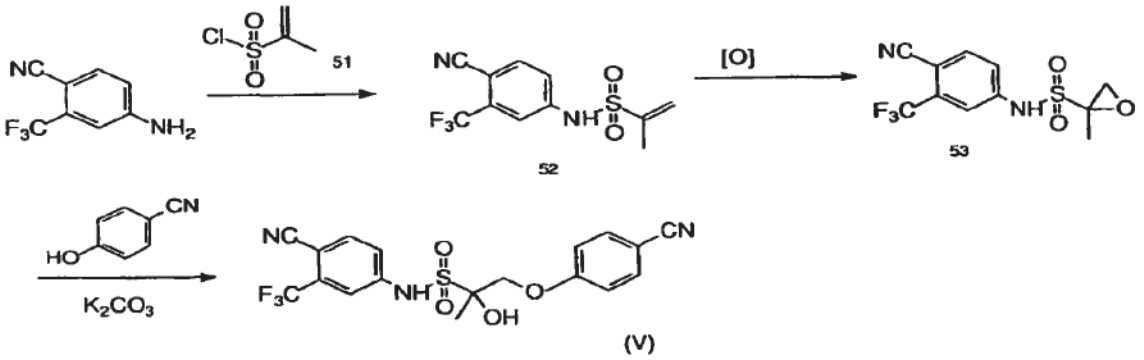

NC
F3C
NH2
Cl
O
S
51
52
[O]
53
HO
CN
K2CO3
OH
(V)

图1C

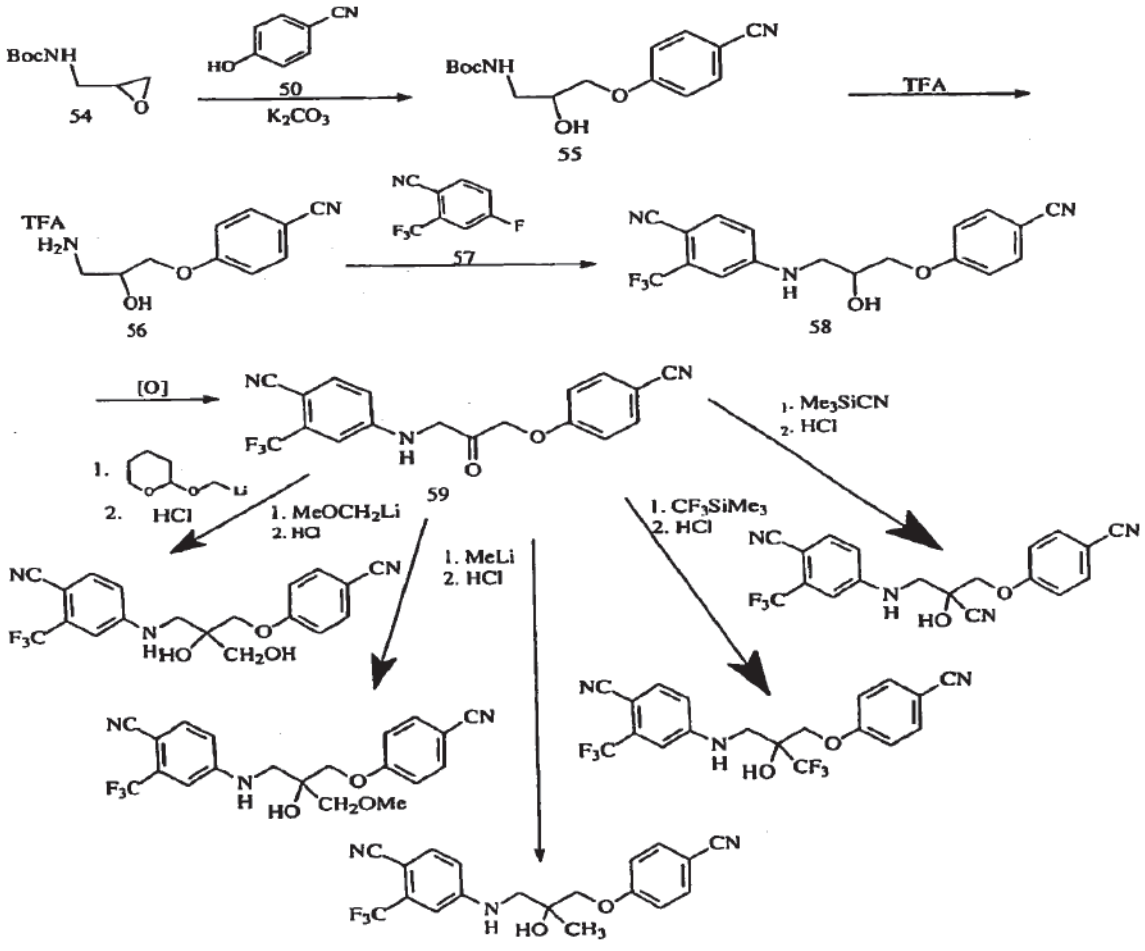

BocNH
54
50
K2CO3
55
TFA
H2N
56
57
58
[O]
59
1. Me3SiCN
2. HCl
1. MeOCH2Li
2. HCl
1. MeLi
2. HCl
1. CF3SiMe3
2. HCl
CH2OH
CH2OMe
CF3
CH3

图1D

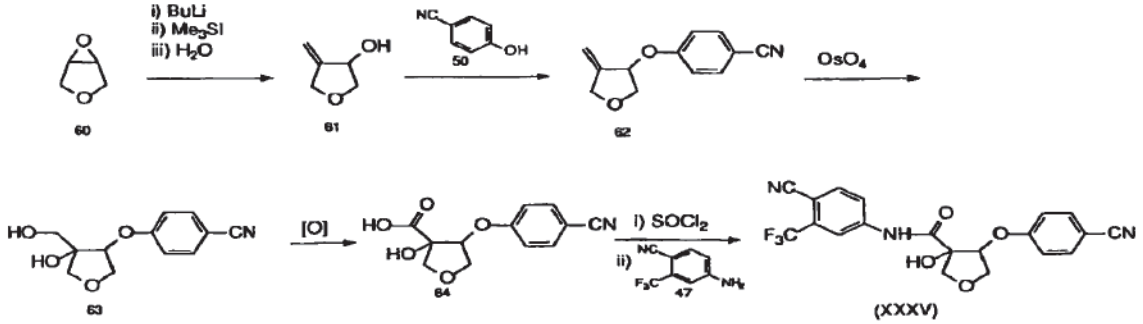



图1E

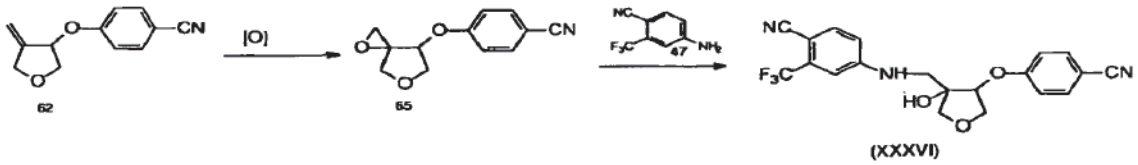



图1F

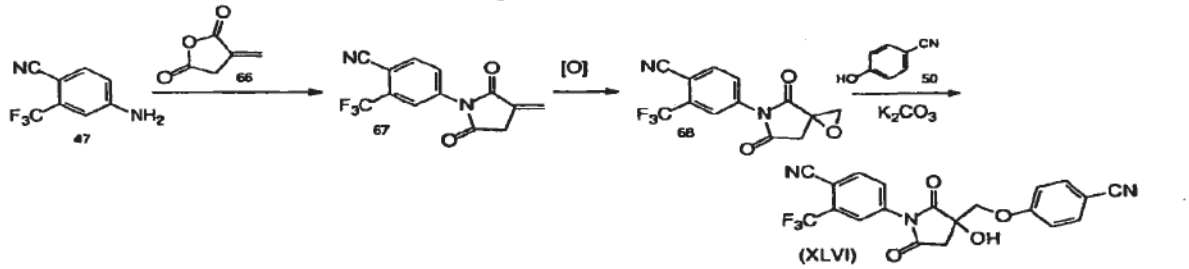



图1G

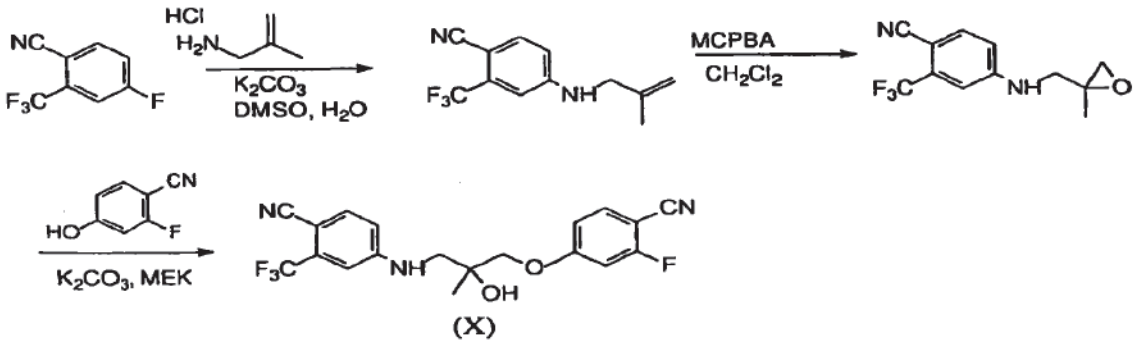
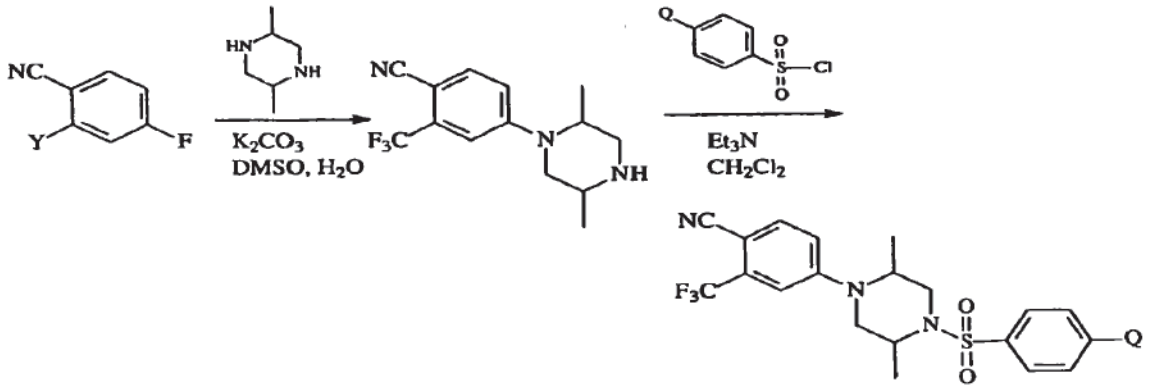
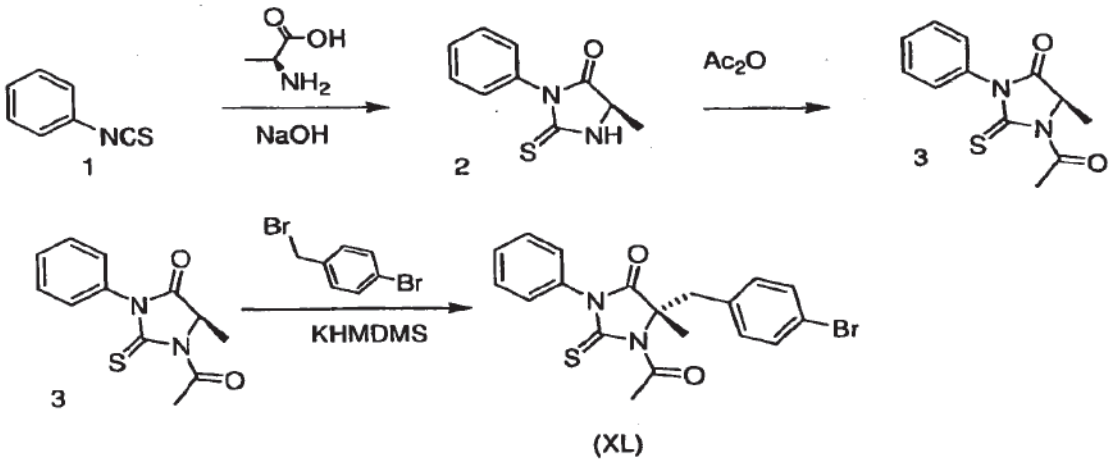



图1H




Q=CN, Y=$CF_3$ (化合物XXIV)
Q=CN, Y=Cl (化合物XXV)
Q=Cl, Y=CN (化合物XXVI)
Q=$CF_3$, Y=Cl (化合物XXVII)
Q=$CF_3$, Y=$CF_3$ (化合物XXVIII)

图1I




(XL)

图1J

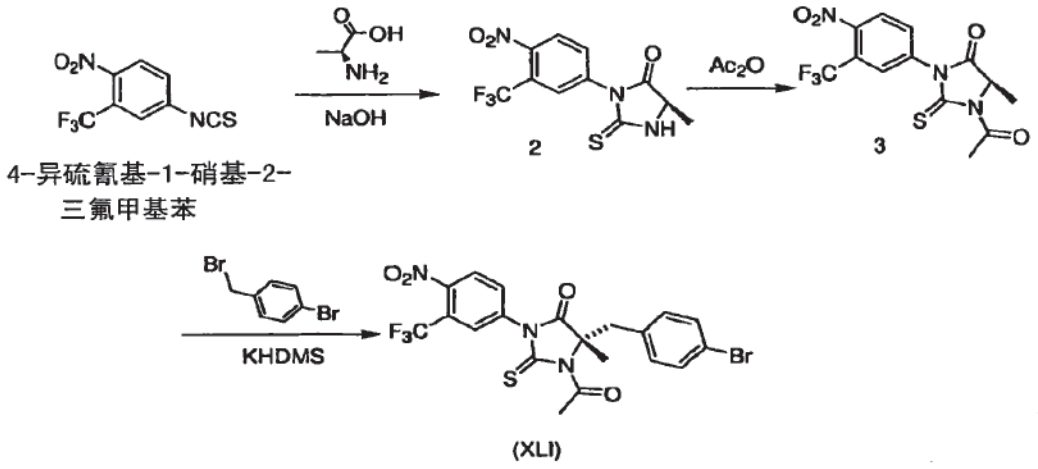
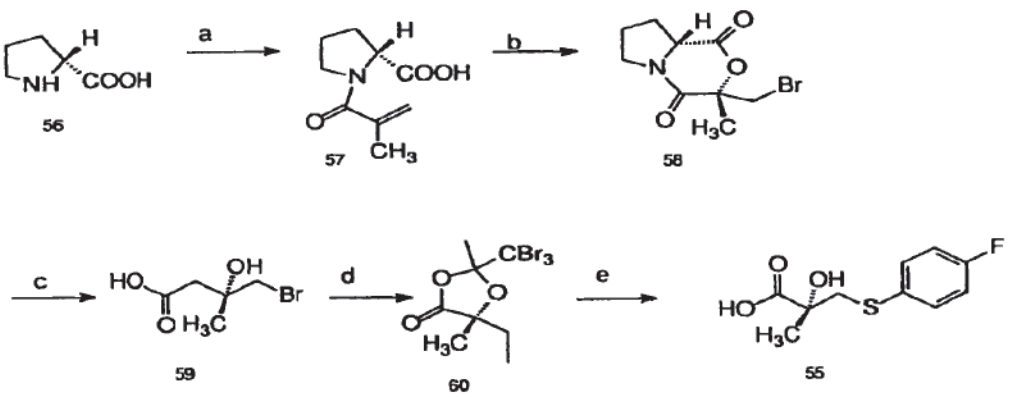
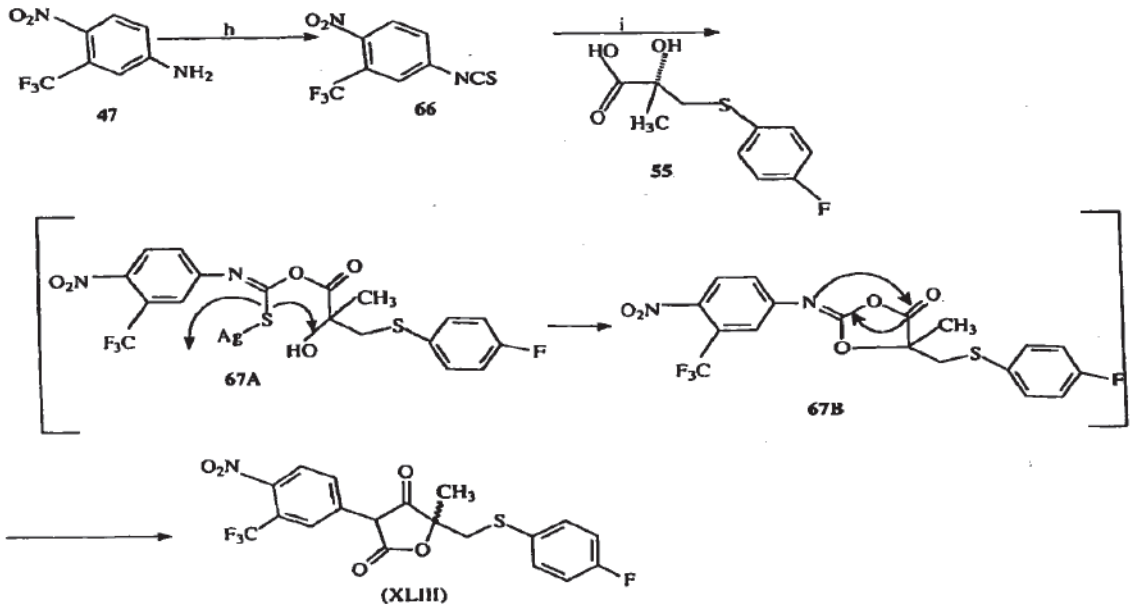

O2N
F3C
NCS
4-异硫氰基-1-硝基-2-
三氟甲基苯
OH
NH2
NaOH
2
Ac2O
3
Br
Br
KHDMS
(XLI)

图1K



试剂： a -异丁烯酰氯、NaOH、丙酮； b-NBS、DMF； c-24%HBr；
d-三溴乙醛、浓硫酸； e- (1) NaOH、4-氟苯硫酚、2-丙醇， (2) 浓HCl。



试剂：h-硫光气、氯仿、NaCO3， i-三氟乙酸银、三乙胺、乙腈。

图2

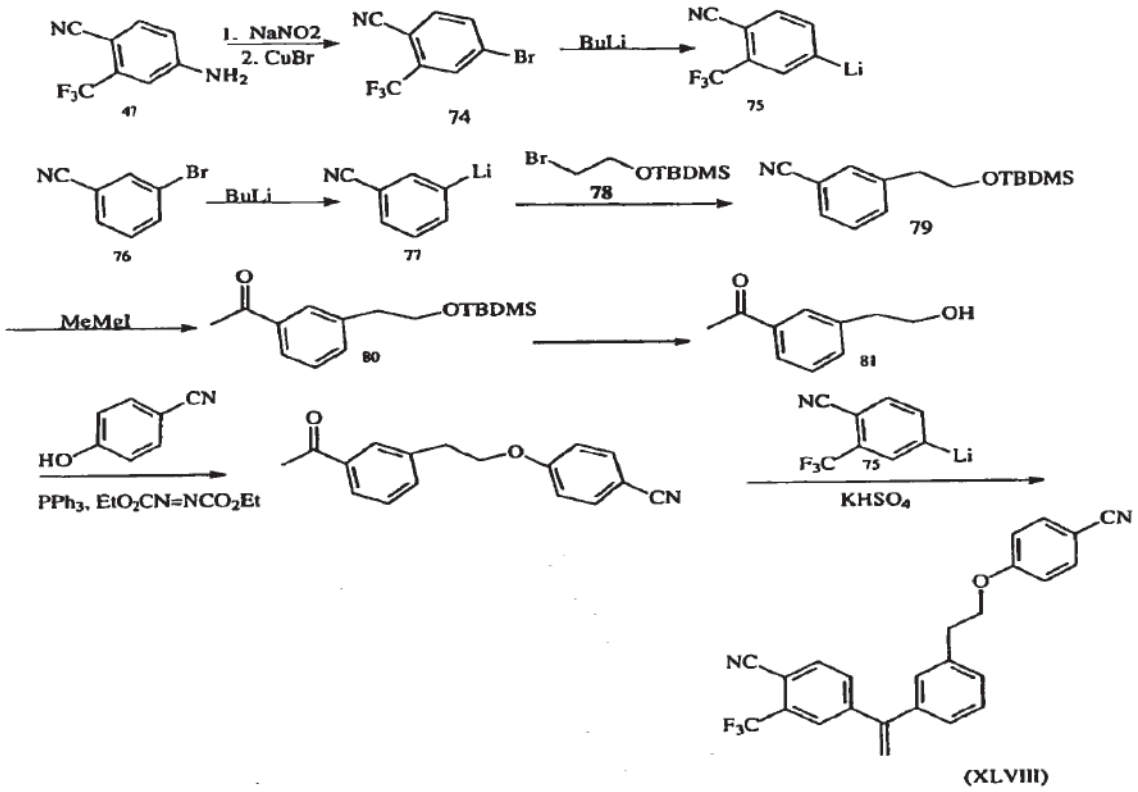

NC
F3C
NH2
47
1. NaNO2
2. CuBr
Br
74
BuLi
Li
75
76
77
78
OTBDMS
79
MeMgI
80
OH
81
HO
CN
PPh3, EtO2CN=NCO2Et
KHSO4
(XLVIII)

图3

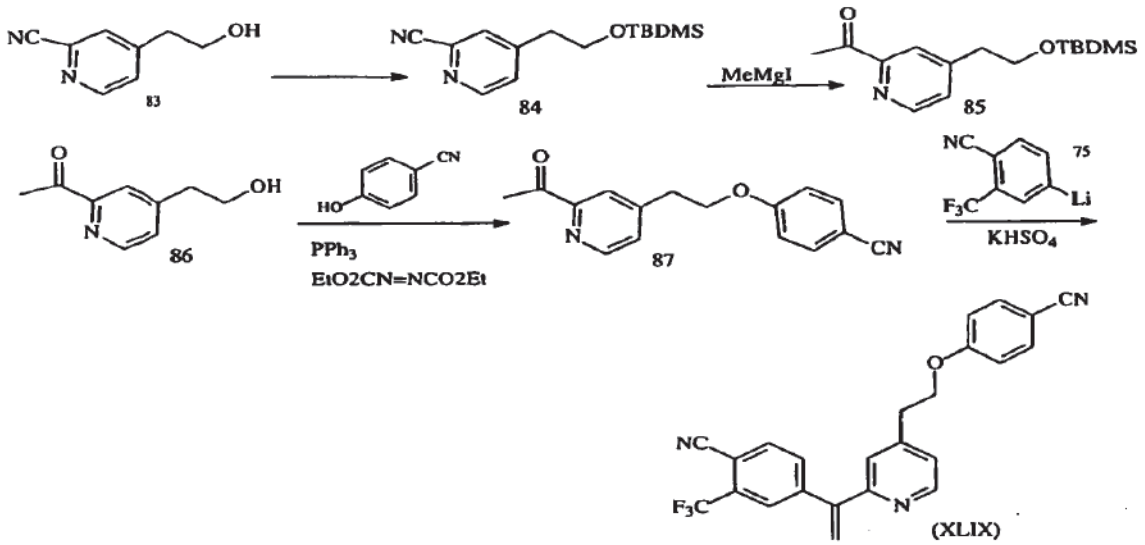

NC
OH
N
83
NC
OTBDMS
N
84
MeMgI
O
OTBDMS
N
85
O
OH
N
86
HO
CN
PPh3
EtO2CN=NCO2Et
O
N
O
CN
87
NC
75
F3C
Li
KHSO4
CN
O
NC
F3C
N
(XLIX)

图4

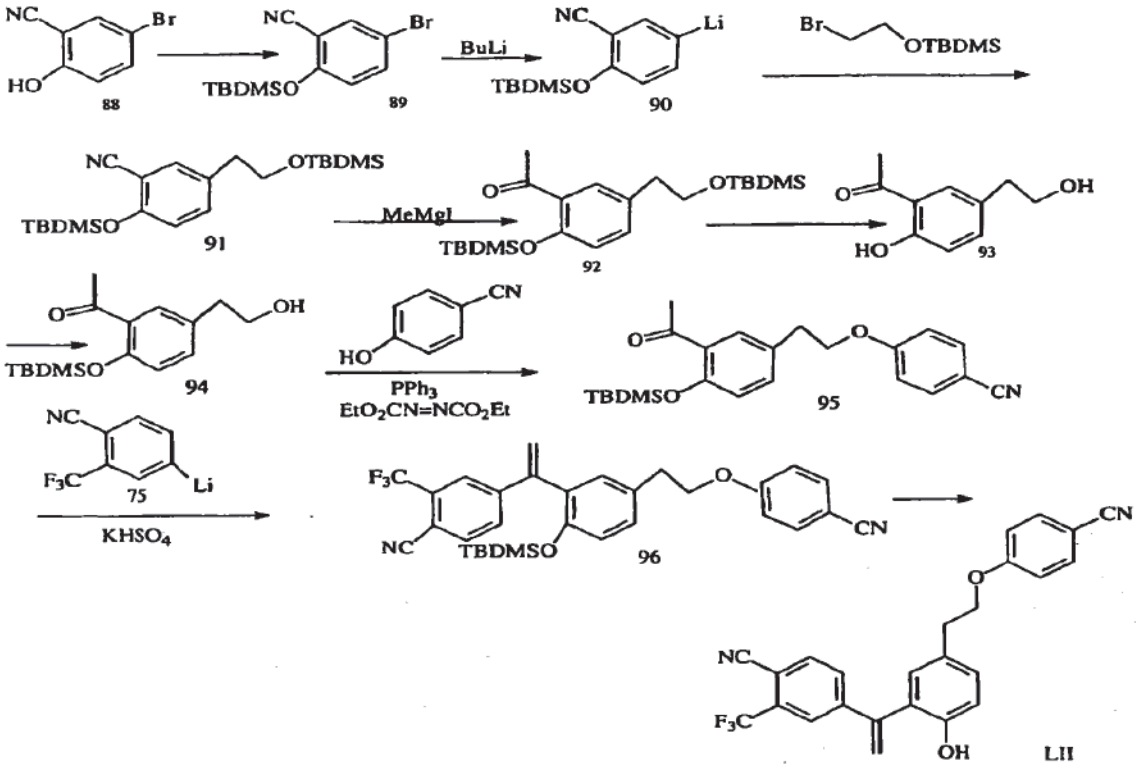

NC
Br
HO
88
TBDMSO
89
BuLi
Li
90
OTBDMS
91
MeMgI
92
OH
93
94
CN
PPh3
EtO2CN=NCO2Et
95
F3C
75
KHSO4
96
LII

图5

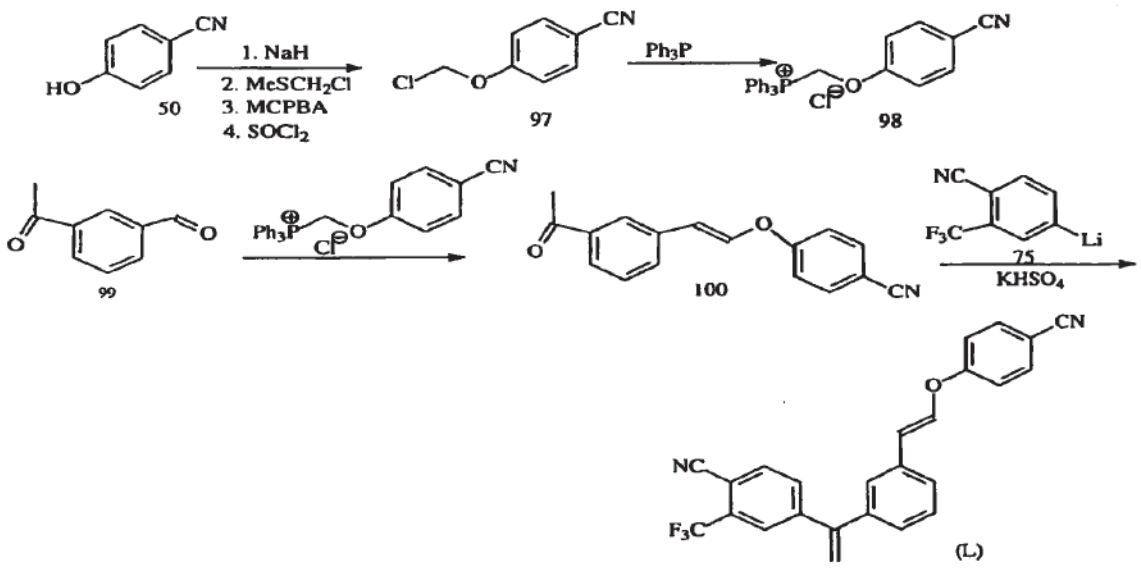

CN
HO
50
1. NaH
2. MeSCH2Cl
3. MCPBA
4. SOCl2
Cl
O
97
Ph3P
Ph3P
Cl
98
99
100
NC
F3C
Li
75
KHSO4
(L)

图6

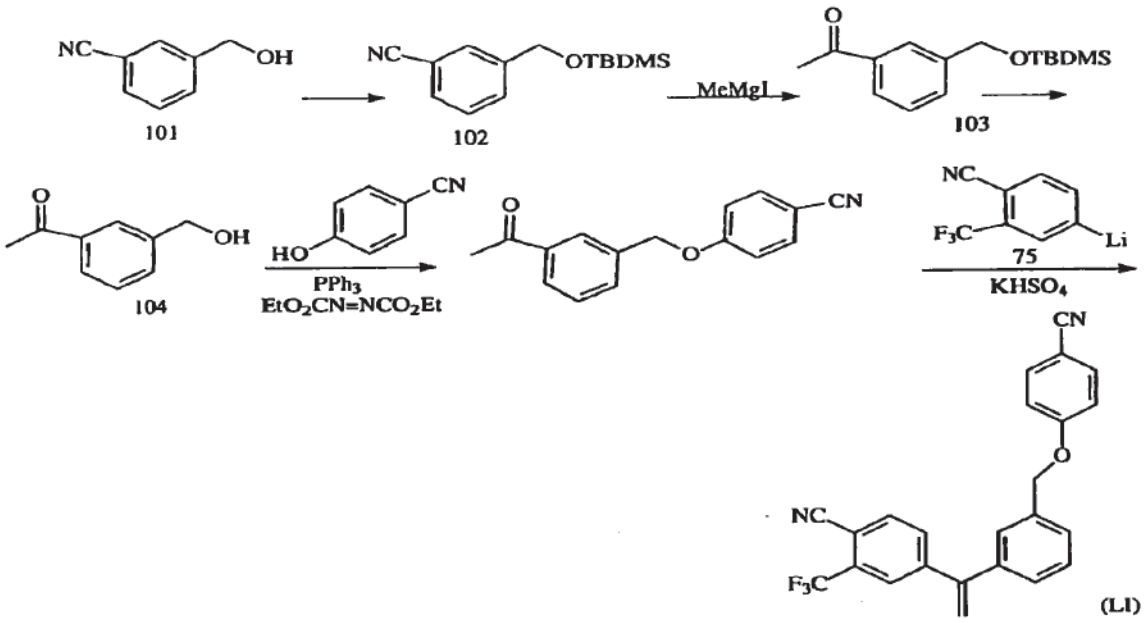

NC
OH
101
NC
OTBDMS
102
MeMgI
O
OTBDMS
103
O
OH
104
HO
CN
PPh3
EtO2CN=NCO2Et
O
CN
O
NC
F3C
Li
75
KHSO4
CN
O
NC
F3C
(LI)

图7

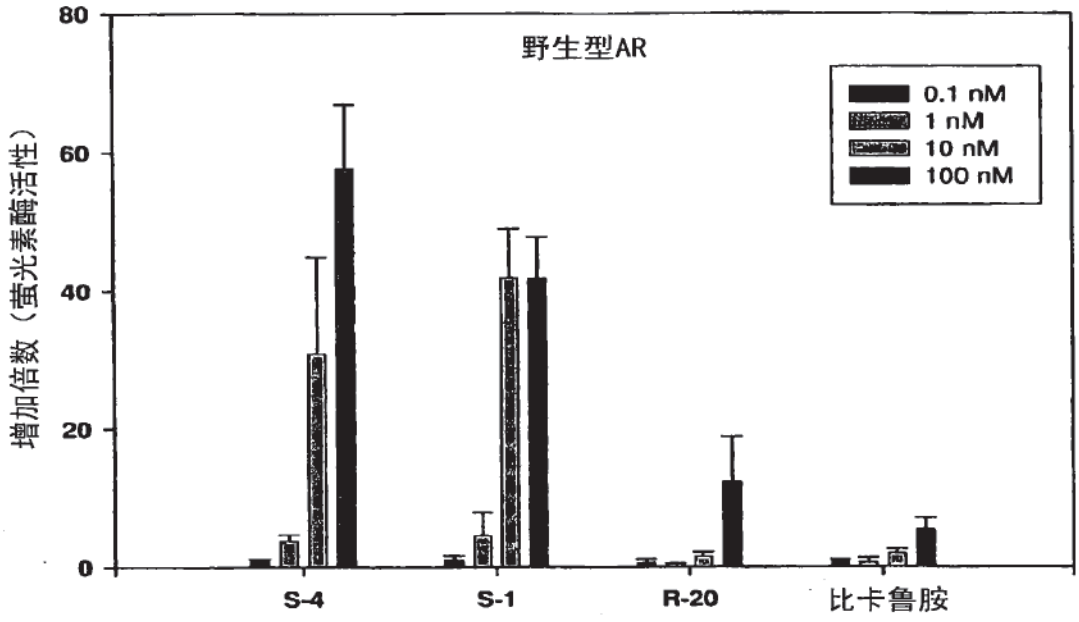

野生型AR
0.1 nM
1 nM
10 nM
100 nM
增加倍数（萤光素酶活性）
80
60
40
20
0
S-4
S-1
R-20
比卡鲁胺

图8

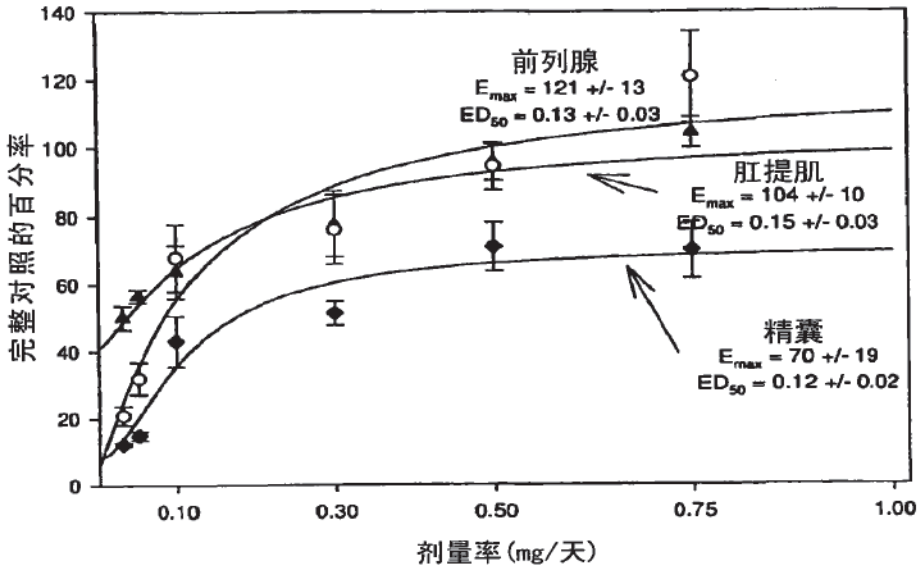

140
120
100
80
60
40
20
0
完整对照的百分率
前列腺
$E_{max}$ = 121 +/- 13
$ED_{50}$ = 0.13 +/- 0.03
肛提肌
$E_{max}$ = 104 +/- 10
$ED_{50}$ = 0.15 +/- 0.03
精囊
$E_{max}$ = 70 +/- 19
$ED_{50}$ = 0.12 +/- 0.02
0.10
0.30
0.50
0.75
1.00
剂量率(mg/天)

图9A

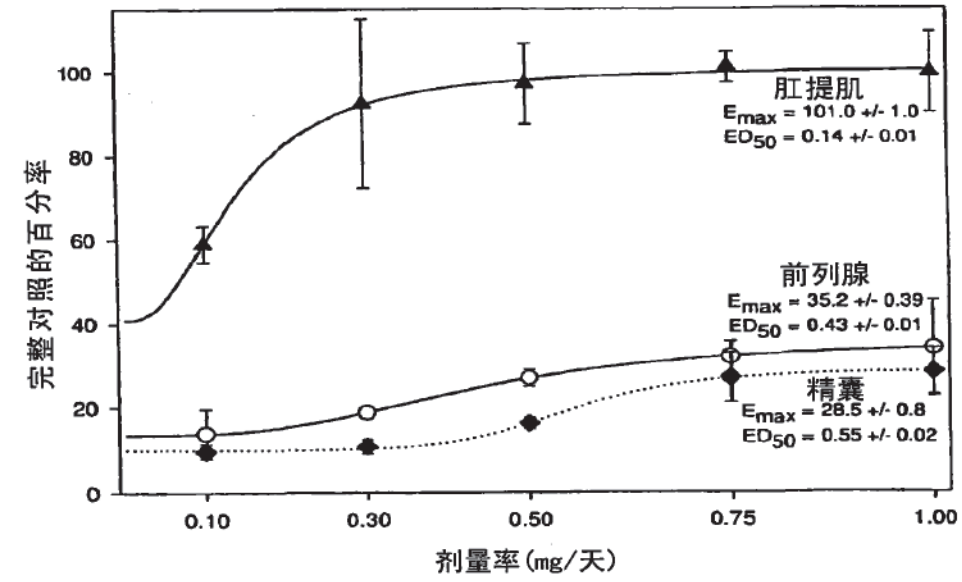

100
80
60
40
20
0
完整对照的百分率
肛提肌
$E_{max}$ = 101.0 +/- 1.0
$ED_{50}$ = 0.14 +/- 0.01
前列腺
$E_{max}$ = 35.2 +/- 0.39
$ED_{50}$ = 0.43 +/- 0.01
精囊
$E_{max}$ = 28.5 +/- 0.8
$ED_{50}$ = 0.55 +/- 0.02
0.10
0.30
0.50
0.75
1.00
剂量率(mg/天)

图9B

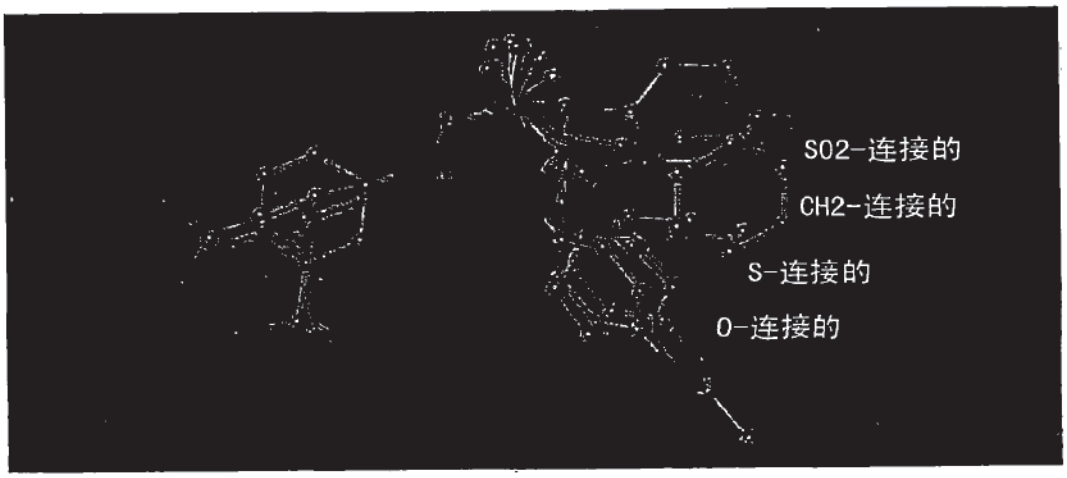



图10

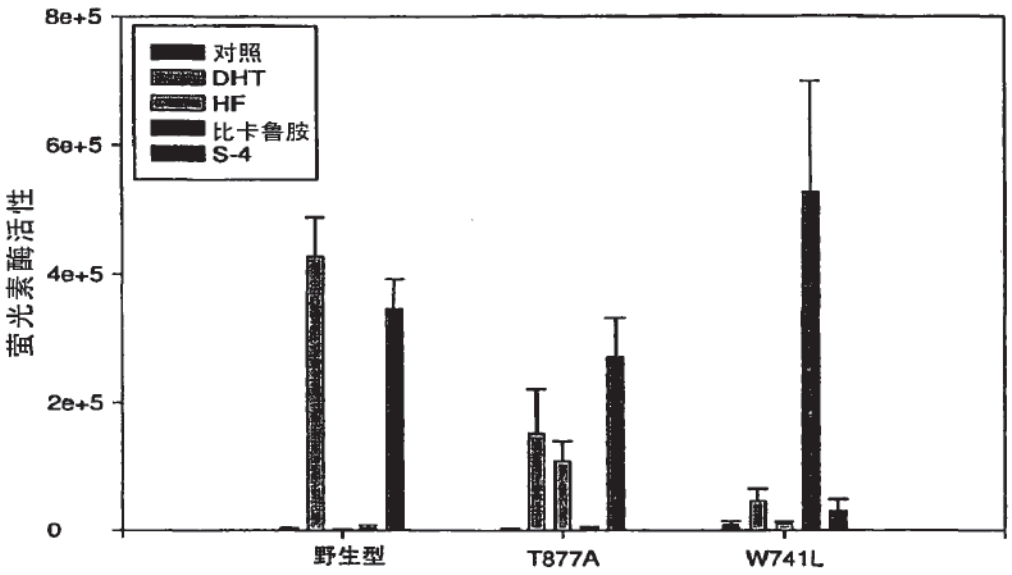



图11

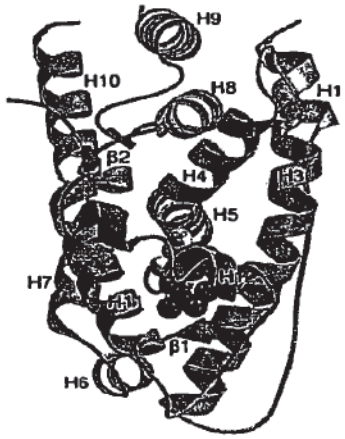

H9
H10
H8
H1
β2
H4
H3
H5
H7
H11
H12
β1
H6

图12A

Met742
Arg752
Thr877
Leu704
Asn705

图12B

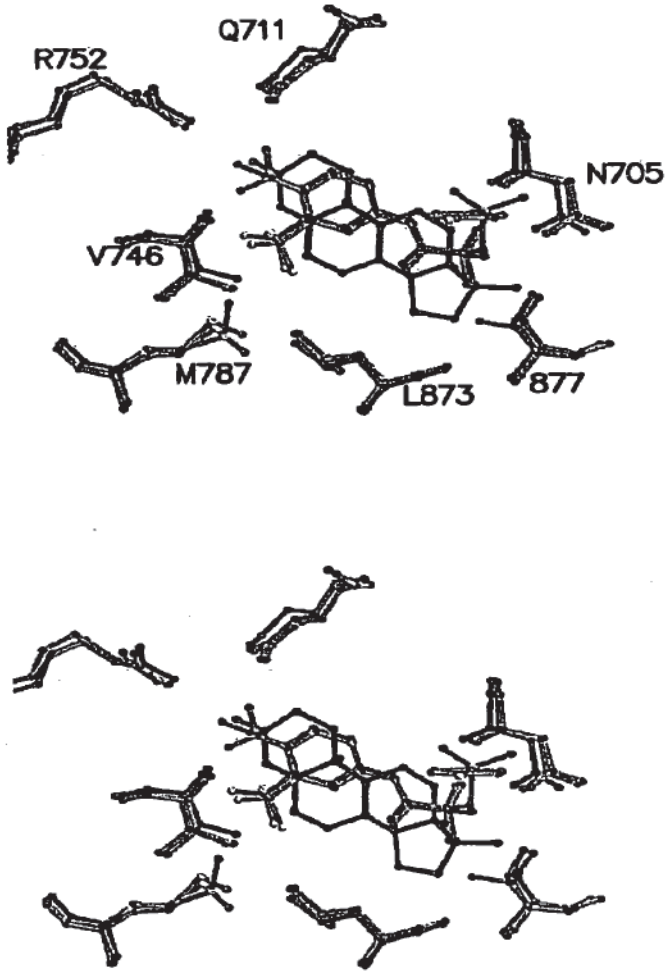



图13A

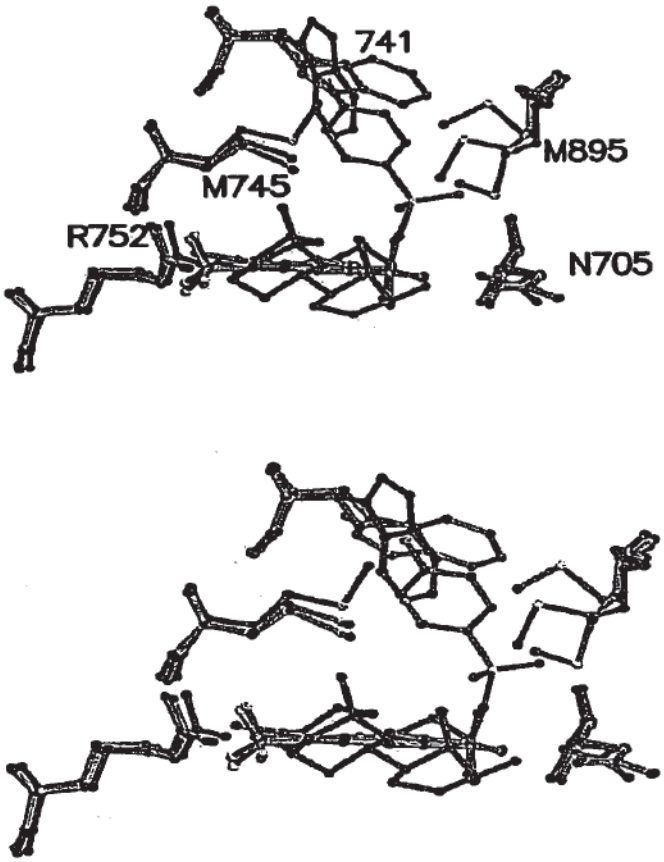



图13B

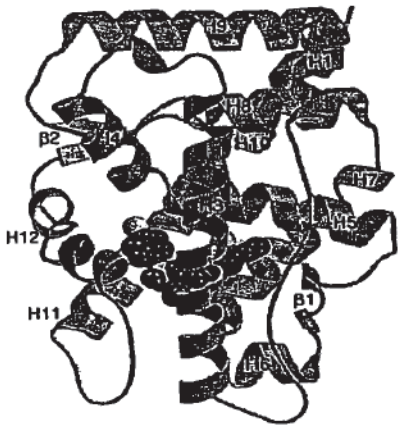

H9
H1
H8
H10
β2
H4
H7
H3
H5
H12
H11
β1
H6

图14A

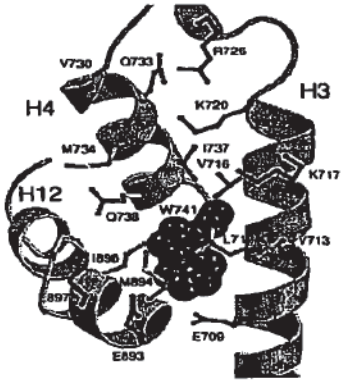

V730
Q733
R726
H4
H3
K720
M734
I737
V716
K717
H12
Q738
W741
L71
V713
I896
M894
E897
E709
E893

图14B

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-20110136865 | 06-09-2011 | BUNTINX; Erik | |
| | 002 | US-20220133742 | 05-05-2022 | GHOSH; Sangita et al. | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | 001 | CN-101516835-A | 08-26-2009 | OSURF OHIO STATE UNIVERSITY RE [US] | Abstract: | ☒ |
| | 002 | WO-2005020910-A2 | 03-10-2005 | PHARMACIA CORP [US], et al. | | ☐ |
| | 003 | WO-2013160317-A2 | 10-31-2013 | HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE] | | ☐ |

| Examiner Signature | | Date Considered | |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

| Complete if Known | |
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| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | DO, Hien-Quang et. al; Copper-catalyzed arylation of C-H bonds; Abstracts of Papers, 236th ACS National Meeting, New Orleans, LA, Apr. 6-10, 2008, Accession No. 2008:390596. | ☐ |
| | 002 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review of U.S. Patent No. 11,007,201 dated December 1, 2023 (pp. 1-38) (PGR2022-00025). | ☐ |
| | 003 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 10,849,908 dated May 28, 2021 (pp. 1-90) (PGR2021-00088). | ☐ |
| | 004 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 11,007,201 dated February 18, 2022 (pp 1-92) (PGR2022-00025). | ☐ |
| | 005 | U.S. Serial No. 16/639,541 Office Action dated April 4, 2022. | ☐ |
| | 006 | U.S. Serial No. 17/586,228 Office Action dated March 30, 2022. | ☐ |

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Sheet 3 of 4

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| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

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## SIGNATURE

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| | | | |
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| Signature | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2024-07-12 |
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

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(54) Title: COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

(57) Abstract: The present invention provides compositions and methods for the treatment of ischemic mediated central nervous system disorder or injury. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic mediated disorder or injury comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

WO 2005/020910 A2

# COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

## FIELD OF THE INVENTION

[0001] The present invention provides compositions and methods for the treatment of reduced blood flow to the central nervous system. More particularly, the invention is directed toward a combination therapy for the treatment or prevention of ischemic-mediated central nervous system disorders or injury, including ischemic stroke, comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor in combination with a corticotropin releasing factor antagonist.

## BACKGROUND OF THE INVENTION

[0002] The continued increase in the incidence of ischemic-mediated central nervous system damage, including ischemic stroke, provides compelling evidence that there is a continuing need for better treatment strategies. Stroke, for example, is consistently the second or the third leading cause of death annually and the leading producer of disability among adults in the United States and western countries. Moreover, roughly 10% of patients with stroke become heavily handicapped, often needing attendant care.

[0003] The pathology underlying ischemic-mediated central nervous system injury has been elucidated. Generally speaking, the normal amount of perfusion to brain gray matter is 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs only when the flow of blood falls below a certain level (approximately 8-10 mL/100 g of brain tissue/min), while at slightly higher levels the tissue remains alive but not able to function. For example, most strokes culminate in a core area of cell death (infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20 percent of normal or less. Without neuroprotective agents, nerve cells facing 80 to 100 percent ischemia will be irreversibly damaged within a few minutes. Surrounding the ischemic core is another area of tissue called the "ischemic penumbra" or "transitional zone" in which cerebral blood flow is between 20 and 50 percent of normal. Cells in this area are endangered, but not yet irreversibly damaged. Thus in the acute stroke, the affected central core brain tissue may die while the more peripheral tissues

remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives.

[0004] At the cellular level, if left untreated, brain or spinal cell injury and death progress in a stepwise manner rapidly within the core infarction, and over time within the ischemic penumbra. Without adequate blood supply, brain or spinal cells lose their ability to produce energy, particularly adenosine triphosphate (ATP). When this energy failure occurs, brain or spinal cells become damaged and will die if critical thresholds are reached. Immediate cell death within the ischemic core is typically necrotic, while cell death in the penumbra may be either necrotic or apoptotic. It is believed that there are an immense number of mechanisms at work causing brain or spinal cell damage and death following energy failure. Each of these mechanisms represents a potential route for intervention. One of the ways brain cells respond to energy failure is by elevating the concentration of intracellular calcium. Worsening this and driving the concentrations to dangerous levels is the process of excitotoxicity, in which brain cells release excessive amounts of glutamate, a neurotransmitter. This stimulates chemical and electrical activities in receptors on other brain cells, which leads to the degradation and destruction of vital cellular structures. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischemic cascade.

[0005] No drug therapy has yet been proven completely effective in preventing brain damage from cerebral ischemia. Interventions have been directed toward salvaging the ischemic penumbra and reducing its size. Restoration of blood flow is the first step toward rescuing the tissue within the penumbra. Therefore, timely recanalization of an occluded vessel to restore perfusion in both the penumbra and in the ischemic core is one treatment option employed. Partial recanalization also markedly reduces the size of the penumbra as well. Moreover, intravenous tissue plasminogen activator and other thrombolytic agents have been shown to have clinical benefit if they are administered within a few hours of symptom onset. Beyond this narrow time window, however, the likelihood of beneficial effects is reduced and hemorrhagic complications related to thrombolytic agents become excessive, seriously compromising their therapeutic value. Hypothermia decreases the size of the ischemic insult in both anecdotal clinical and laboratory reports. In addition, a wide variety of agents have been shown to reduce infarct volume in animal models. These agents

include pharmacologic interventions that involve thrombolysis, calcium channel blockade, and cell membrane receptor antagonism have been studied and have been found to be beneficial in animal cortical stroke models. But there is a continuing need for improved treatment regimens following ischemic-mediated central nervous system injury.

[0006] Corticotropin releasing factor ("CRF"), also referred to as corticotropin releasing hormone ("CRH"), is a 41 amino acid neuropeptide hormone. This peptide is the major physiologic regulator of the basal and stress-induced production and release of adrenocorticotropic hormone ("ATCH"), $\beta$-endorphin, and other peptides from the pituitary via binding of CRF to its several receptors. ACTH release leads to the release of cortisol and other adrenal steroids. Important functions affected by the action of CRF include behavior, temperature regulation, food intake, reproduction, memory and learning, and can also induce seizures (Wong et al., *NeuroReport*, 6:13 (1995) 1785-1788 Increasing evidence exists to implicate the involvement of CRF in the pathogenesis of ischemic brain damage (Mackay et al., J. Cerebral Blood Flow and Metabolism (2001) 21:1208-1214; and DeVries et al. *Proc. Nat'l. Academy Science*, (2001) 98:11824-11828). CRF has also been implicated as being neurotoxic, being involved in neurodegeneration following cerebral ischemia (Lyons et al., *Brain Research*, 545 (1991) 339-342); Wong et al. (1995)). Additionally, several authors have noted that in humans, post-stroke concentrations of cortisol are predictive of stoke outcome, high cortisol concentrations being associated with increased morbidity and mortality (Feibel et al., *JAMA* (1977) 238: 1374-1376; Olsson, t., *J. Int. Med.* (1990) 228: 177-181).

[0007] Several recent studies have found that the administration of a corticotropin releasing factor antagonist reduces the extent of stroke-induced brain damage when administered to a subject shortly before or after the onset of the ischemic cascade. In one study, it was shown that a low dose of the corticotropin releasing factor antagonist $\alpha$-helical CRF 9-41 in combination with a vehicle administered via injection either 30 minutes before or 10 minutes after a unilateral, permanent middle cerebral artery occlusion (MCAo) could markedly inhibit (by over 60%) the volume of the infarction (Strijbos, et al., *Brain Research*, 656 (1994) pp. 405-408). Corticotropin releasing factor antagonists, and in particular $\alpha$-helical CRF, have also been found to demonstrate a neuroprotective effect in a dose-dependent manner (Lyons et al. (1991)). In addition, it appears that corticotropin releasing factor antagonists demonstrate an

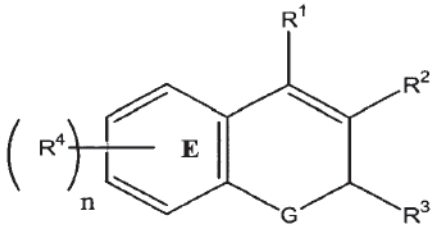
ability to inhibit neuronal damage induced by pharmacological activation of NMDA receptors , particularly in the striatum, indicating that NMDA receptor-mediated neurotoxicity is at least in part due to the release of endogenous corticotropin releasing factor (Strijbos et al. (1994)).

[0008] Moreover, several studies indicate that cyclooxygenase-2 is involved in the inflammatory component of the ischemic cascade. Cyclooxygenase-2 expression is known to be induced in the central nervous system following ischemic injury. In one study, it was shown that treatment with a cyclooxygenase-2 selective inhibitor reduced infarct volume in mice subjected to ischemic brain injury (Nagayama et al., (1999) J. Cereb. Blood Flow Metab.19(11):1213-19). A similar study showed that cyclooxygenase-2 deficient mice have a significant reduction in brain injury produced by occlusion of the middle cerebral artery when compared to mice that express cyclooxygenase-2 (Iadecola et al., (2001) PNAS 98:1294-1299). Another study demonstrated that treatment with cyclooxygenase-2 selective inhibitor results in improved behavioral deficits induced by reversible spinal ischemia in rabbits (Lapchak et al., (2001) Stroke 32(5):1220-1230).

## SUMMARY OF THE INVENTION

[0009] Among the several aspects of the invention is provided a method for the treatment of ischemic mediated central nervous system disorders in a subject. The method comprises administering to the subject a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof in combination with a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

[0010] In one embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof is a member of the chromene class of compounds. For example, the chromene compound may be a compound of the formula




(I)

[0011] wherein:

[0012] n is an integer which is 0, 1, 2, 3 or 4;

[0013] G is O, S or $NR^a$;

[0014] $R^a$ is alkyl;

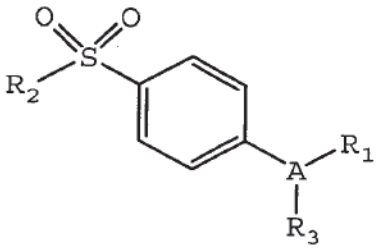
[0015] $R^1$ is H or aryl;

[0016] $R^2$ is carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl or alkoxycarbonyl;

[0017] $R^3$ is haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro or alkylsulfonyl; and

[0018] each $R^4$ is independently H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, or alkylcarbonyl; or wherein $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0019] In another embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof comprises a compound of the formula




[0020] wherein:

[0021] A is a partially unsaturated or unsaturated heterocyclyl ring or a partially unsaturated or unsaturated carbocyclic ring;

[0022] $R_1$ is heterocyclyl, cycloalkyl, cycloalkenyl or aryl, wherein $R_1$ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0023] $R^2$ is methyl or amino; and

[0024] $R^3$ is H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, or N-alkyl-N-arylaminosulfonyl.

[0025] In yet another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of $\alpha$-helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919.

[0026] Other aspects of the invention are described in more detail below.

## ABBREVIATIONS AND DEFINITIONS

[0027] The term "acyl" is a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and trifluoroacetyl.

[0028] The term "alkenyl" is a linear or branched radical having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl" also are radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0029] The terms "alkoxy" and "alkyloxy" are linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[0030] The term "alkoxyalkyl" is an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[0031] The term "alkoxycarbonyl" is a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[0032] Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" is a linear, cyclic or branched radical having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0033] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

[0034] The term "alkylaminoalkyl" is a radical having one or more alkyl radicals attached to an aminoalkyl radical.

[0035] The term "alkylaminocarbonyl" is an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

[0036] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl

radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[0037] The term "alkylthio" is a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[0038] The term "alkylthioalkyl" is a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[0039] The term "alkylsulfinyl" is a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[0040] The term "alkynyl" is a linear or branched radical having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0041] The term "aminoalkyl" is an alkyl radical substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

[0042] The term "aminocarbonyl" is an amide group of the formula -C(=O)NH2.

[0043] The term "aralkoxy" is an aralkyl radical attached through an oxygen atom to other radicals.

[0044] The term "aralkoxyalkyl" is an aralkoxy radical attached through an oxygen atom to an alkyl radical.

[0045] The term "aralkyl" is an aryl-substituted alkyl radical such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl

may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[0046] The term "aralkylamino" is an aralkyl radical attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" are amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[0047] The term "aralkylthio" is an aralkyl radical attached to a sulfur atom.

[0048] The term "aralkylthioalkyl" is an aralkylthio radical attached through a sulfur atom to an alkyl radical.

[0049] The term "aroyl" is an aryl radical with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[0050] The term "aryl", alone or in combination, is a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[0051] The term "arylamino" is an amino group, which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

[0052] The term "aryloxyalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

[0053] The term "arylthioalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[0054] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", is -(C=O)-.

[0055] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", is -CO2H.

[0056] The term "carboxyalkyl" is an alkyl radical substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which are lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

[0057] The term "corticotropin releasing factor" and "corticotropin releasing hormone" both refer to the same 41 amino acid polypeptide as described herein and are used interchangeably without consequence.

[0058] The term "corticotropin releasing factor antagonist" or alternatively "corticotropin releasing hormone antagonist" is any peptide or non-peptide substance that tends to nullify the action of corticotropin releasing factor or that binds to a cell receptor to which corticotropin releasing factor would otherwise be able to bind and does not elicit a biological response. Corticotropin releasing factor antagonists can include, for example, peptide and non-peptide antagonists, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems. Specific examples of such corticotropin releasing factor antagonists include, for example, $\alpha$-helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919. Furthermore, a corticotropin releasing factor antagonist may bind any of the corticotropin releasing factor receptors, including, for example, $CRF_1$, $CRF_2$, and CRF-BP receptors.

[0059] The term "cycloalkenyl" is a partially unsaturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

[0060] The term "cycloalkyl" is a saturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0061] The term "cyclooxygenase-2 selective inhibitor" is a compound able to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Typically, it includes compounds that have a cyclooxygenase-2 $IC_{50}$ of less than about 0.2 micro molar, and also have a selectivity ratio of cyclooxygenase-1 (COX-1) $IC_{50}$ to cyclooxygenase-2 (COX-2) $IC_{50}$ of at least about 5, more typically of at least about 50, and even more typically, of at least about 100. Moreover, the cyclooxygenase-2 selective inhibitors as

described herein have a cyclooxygenase-1 $IC_{50}$ of greater than about 1 micro molar, and more preferably of greater than 10 micro molar. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

[0062] The term "halo" is a halogen such as fluorine, chlorine, bromine or iodine.

[0063] The term "haloalkyl" is a radical wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically included are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" is a radical having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0064] The term "heteroaryl" is an unsaturated heterocyclyl radical. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-

membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also includes radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[0065] The term "heterocyclyl" is a saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[0066] The term "heterocyclylalkyl" is a saturated and partially unsaturated heterocyclyl-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

[0067] The term "hydrido" is a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH2-) radical.

[0068] The term "hydroxyalkyl" is a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0069] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product; that is

the "pharmaceutically acceptable" material is relatively safe and/or non-toxic, though not necessarily providing a separable therapeutic benefit by itself. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzy1ethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0070] The term "prodrug" refers to a chemical compound that can be converted into a therapeutic compound by metabolic or simple chemical processes within the body of the subject. For example, a class of prodrugs of COX-2 inhibitors is described in US Patent No. 5,932,598, herein incorporated by reference.

[0071] The term "subject" for purposes of treatment includes any human or animal subject who is need of treatment for an ischemic mediated central nervous system disorder or injury or who is at risk for developing an ischemic mediated central nervous system disorder or injury. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human being.

[0072] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, is a divalent radical $-SO_2-$. "Alkylsulfonyl" is an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" are $NH_2O_2S-$.

[0073] The phrase "therapeutically-effective" is intended to qualify the amount of each agent (i.e. the amount of cyclooxygenase-2 selective inhibitor and the amount of corticotropin releasing factor antagonist) which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself.

[0074] The term "thrombotic event" or "thromboembolic event" includes, but is not limited to arterial thrombosis, including stent and graft thrombosis, cardiac thrombosis, coronary thrombosis, heart valve thrombosis, pulmonary thrombosis and venous thrombosis. Cardiac thrombosis is thrombosis in the heart. Pulmonary thrombosis is thrombosis in the lung. Arterial thrombosis is thrombosis in an artery. Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or a myocardial infarction. Venous thrombosis is thrombosis in a vein. Heart valve thrombosis is a thrombosis on a heart valve. Stent thrombosis is thrombosis resulting from and/or located in the vicinity of a vascular stent. Graft thrombosis is thrombosis resulting from and/or located in the vicinity of an implanted graft, particularly a vascular graft. A thrombotic event as used herein is meant to embrace both a local thrombotic event and a distal thrombotic event occurring anywhere within the body (e.g., a thromboembolic event such as for example an embolic stroke).

[0075] The term "vaso-occlusive event" includes a partial occlusion (including a narrowing) or complete occlusion of a blood vessel, a stent or a vascular graft. A vaso-occlusive event intends to embrace thrombotic or thromboembolic events, and the vascular occlusion disorders or conditions to which they give rise. Thus, a vaso-occlusive event is intended to embrace all vascular occlusive disorders resulting in partial or total vessel occlusion from thrombotic or thromboembolic events.

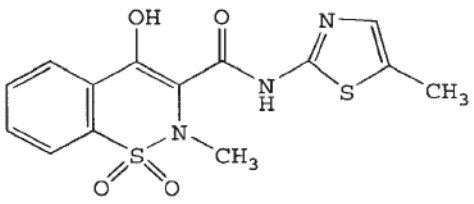
## DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0076] The present invention provides a combination therapy comprising the administration to a subject of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a corticotropin releasing factor antagonist. The combination therapy is used to treat or prevent ischemic mediated central nervous system damage, such as damage to a central nervous system cell resulting from a decrease in blood flow to the cell or damage resulting from a traumatic injury to the cell. In addition, the combination therapy may

also be useful for the treatment of stroke or other vaso-occlusive events. When administered as part of a combination therapy, the COX-2 selective inhibitor together with the corticotropin releasing factor antagonist provide enhanced treatment options as compared to administration of the COX-2 selective inhibitor or the corticotropin releasing factor antagonist alone.

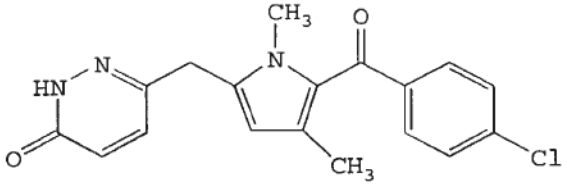
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[0077] A number of suitable cyclooxygenase-2 selective inhibitors or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof, may be employed in the composition of the current invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-1.



B-1

[0078] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-2.

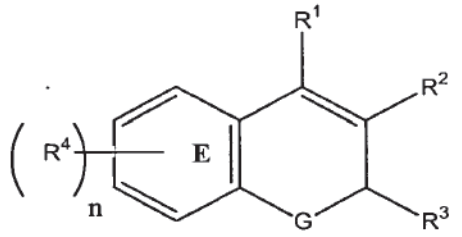


B-2

[0079] In still another embodiment the cyclooxygenase-2 selective inhibitor is a chromene compound that is a substituted benzopyran or a substituted benzopyran analog, and even more typically, selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, dihydronaphthalenes or a compound having

[0080] Formula *I* shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

[0081] In another embodiment, the cyclooxygenase-2 selective inhibitor is a chromene compound represented by Formula *I* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:




*(I)*

[0082] wherein:

[0083] n is an integer which is 0, 1, 2, 3 or 4;

[0084] G is O, S or $NR^a$;

[0085] $R^a$ is alkyl;

[0086] $R^1$ is selected from the group consisting of H and aryl;

[0087] $R^2$ is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0088] $R^3$ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0089] each $R^4$ is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0090] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0091] wherein:

[0092] n is an integer which is 0, 1, 2, 3 or 4;

[0093] G is O, S or $NR^a$;

[0094] $R^a$ is alkyl;

[0095] $R^1$ is H;

[0096] $R^2$ is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0097] $R^3$ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0098] each $R^4$ is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0099] In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)*, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0100] wherein:

[0101] n is an integer which is 0, 1, 2, 3 or 4;

[0102] G is oxygen or sulfur;

[0103] $R^1$ is H;

[0104] $R^2$ is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

[0105] $R^3$ is lower haloalkyl, lower cycloalkyl or phenyl; and

[0106] each $R^4$ is independently H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower

alkylcarbonyl; or $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0107] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0108] wherein:

[0109] n is an integer which is 0, 1, 2, 3 or 4;

[0110] G is oxygen or sulfur;

[0111] $R^1$ is H;

[0112] $R^2$ is carboxyl;

[0113] $R^3$ is lower haloalkyl; and

[0114] each $R^4$ is independently H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0115] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0116] wherein:

[0117] n is an integer which is 0, 1, 2, 3 or 4;

[0118] G is oxygen or sulfur;

[0119] $R^1$ is H;

[0120] $R^2$ is carboxyl;

[0121] $R^3$ is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

[0122] each $R^4$ is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-

methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0123] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0124] wherein:

[0125] n is an integer which is 0, 1, 2, 3 or 4;

[0126] G is oxygen or sulfur;

[0127] $R^1$ is H;

[0128] $R^2$ is carboxyl;

[0129] $R^3$ is trifluoromethyl or pentafluoroethyl; and

[0130] each $R^4$ is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, or phenyl; or wherein $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0131] In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0132] wherein:

[0133] n is 4;

[0134] G is O or S;

[0135] $R^1$ is H;

[0136] $R^2$ is $CO_2H$;

[0137] $R^3$ is lower haloalkyl;

[0138] a first $R^4$ corresponding to $R^9$ is hydrido or halo;

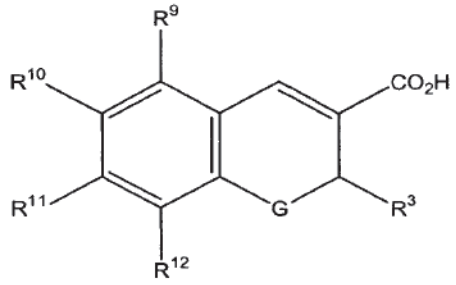
[0139] a second $R^4$ corresponding to $R^{10}$ is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-

membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

[0140] a third $R^4$ corresponding to $R^{11}$ is H, lower alkyl, halo, lower alkoxy, or aryl; and

[0141] a fourth $R^4$ corresponding to $R^{12}$ is H, halo, lower alkyl, lower alkoxy, or aryl;

[0142] wherein Formula *(I)* is represented by Formula *(Ia)*:




*(Ia)*

[0143] The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula *(Ia)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0144] wherein:

[0145] G is O or S;

[0146] $R^3$ is trifluoromethyl or pentafluoroethyl;

[0147] $R^9$ is H, chloro, or fluoro;

[0148] $R^{10}$ is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

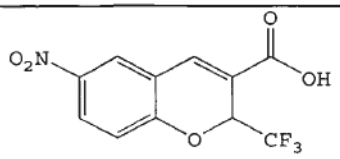
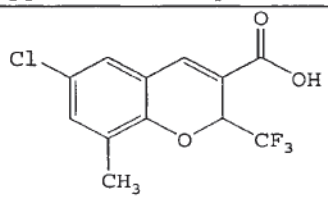
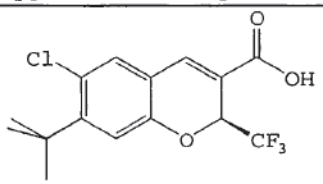
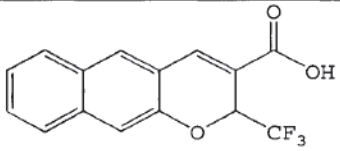
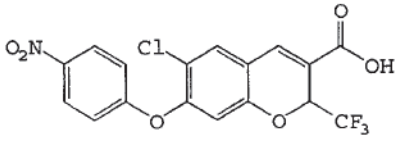
[0149] $R^{11}$ is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

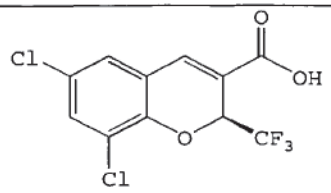
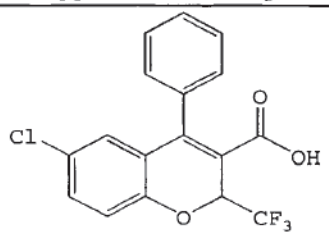
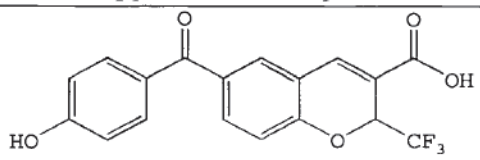
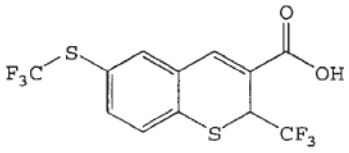
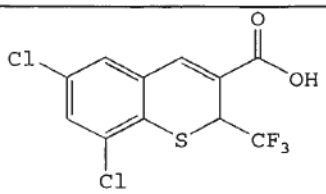
[0150] $R^{12}$ is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

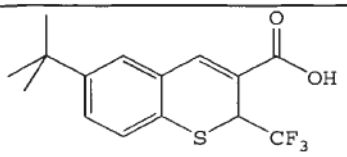
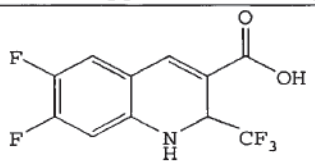
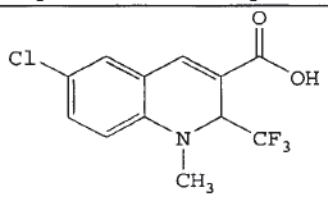
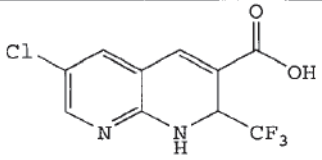
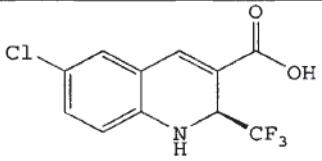
[0151] Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1 below.

TABLE 1

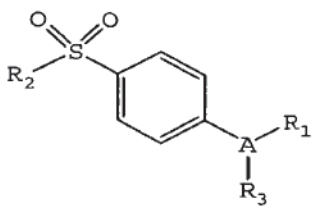
EXAMPLES OF CHROMENE CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

| Compound Number | Structural Formula |
|---|---|
| B-3 |  6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid |
| B-4 |  6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid |
| B-5 |  ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid |
| B-6 |  2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid |
| B-7 |  6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1- benzopyran-3-carboxylic acid |

| Compound Number | Structural Formula |
|---|---|
| B-8 |  ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid |
| B-9 |  6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid |
| B-10 |  6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid |
| B-11 |  2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid |
| B-12 |  6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid |

| Compound Number | Structural Formula |
|---|---|
| B-13 |  6-(1,1-Dimethylethyl)-2-(trifluoromethyl) -2H-1-benzothiopyran-3-carboxylic acid |
| B-14 |  6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid |
| B-15 |  6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid |
| B-16 |  6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid |
| B-17 |  ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid |

[0152] In a further embodiment, the cyclooxygenase-2 selective inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *II* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,



*II*

[0153] wherein:

[0154] A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

[0155] $R^1$ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein $R^1$ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0156] $R^2$ is selected from the group consisting of methyl and amino; and

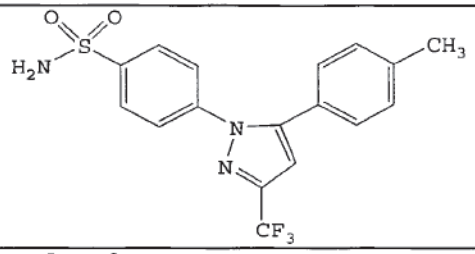
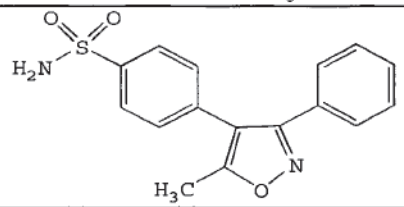
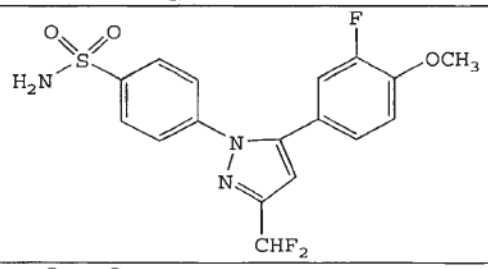
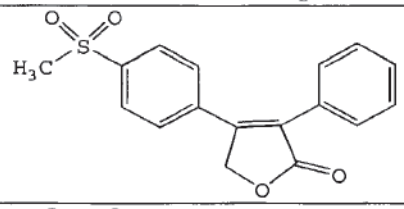
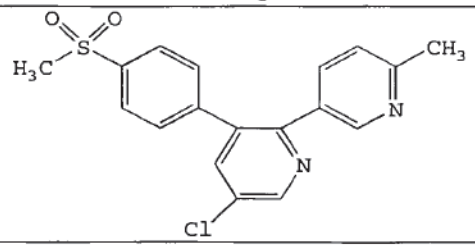
[0157] $R^3$ is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl.

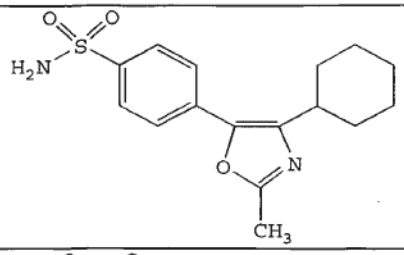
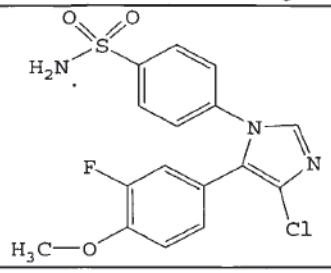
[0158] In another embodiment, the cyclooxygenase-2 selective inhibitor represented by the above Formula *II* is selected from the group of compounds illustrated in Table 2, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7),

deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), tilmacoxib (JTE-522; B-23; CAS No. 180200-68-4), and cimicoxib (UR-8880; B23a; CAS No. 265114-23-6).

TABLE 2

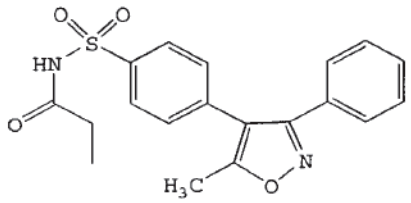
EXAMPLES OF TRICYCLIC CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

| Compound Number | Structural Formula |
|---|---|
| B-18 |  |
| B-19 |  |
| B-20 |  |
| B-21 |  |
| B-22 |  |

| Compound Number | Structural Formula |
|---|---|
| B-23 |  |
| B23a |  |

[0159] In still another embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

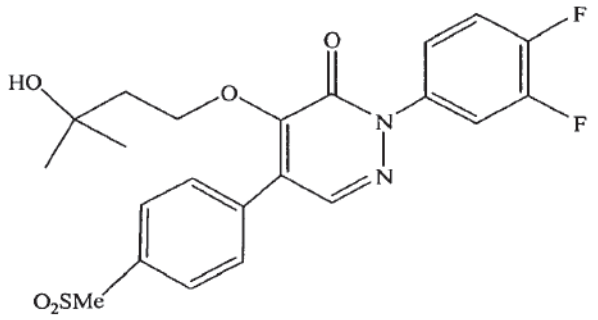
[0160] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



B-24

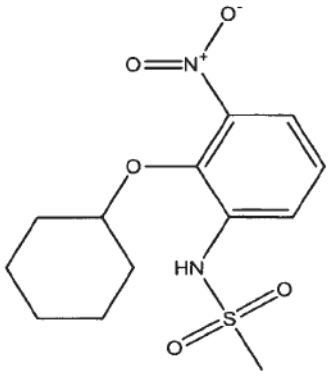
[0161] One form of parecoxib is sodium parecoxib.

[0162] In another embodiment of the invention, the compound having the formula B-25 or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-25 that has been previously described in International Publication number WO 00/24719 (which is herein incorporated by reference) is another tricyclic cyclooxygenase-2 selective inhibitor that may be advantageously employed.



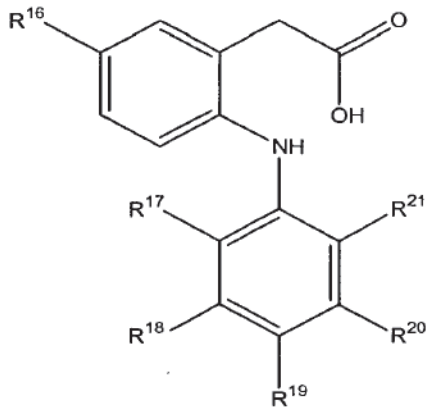

B-25

[0163] Another cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-26.




B-26

[0164] In yet a further embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



*(III)*

[0165] wherein:

[0166] $R^{16}$ is methyl or ethyl;

[0167] $R^{17}$ is chloro or fluoro;

[0168] $R^{18}$ is hydrogen or fluoro;

[0169] $R^{19}$ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

[0170] $R^{20}$ is hydrogen or fluoro; and

[0171] $R^{21}$ is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of $R^{17}$, $R^{18}$, $R^{20}$ and $R^{21}$ is not fluoro when $R^{16}$ is ethyl and $R^{19}$ is H.

[0172] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (lumiracoxib; B-211) and that has the structure shown in Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

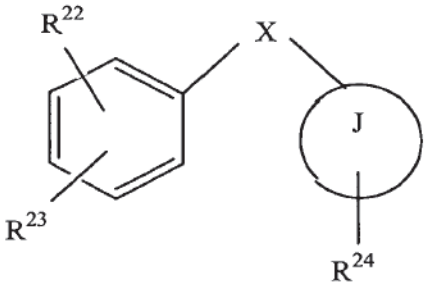
[0173] $R^{16}$ is ethyl;

[0174] $R^{17}$ and $R^{19}$ are chloro;

[0175] $R^{18}$ and $R^{20}$ are hydrogen; and

[0176] $R^{21}$ is methyl.

[0177] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula *(IV)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:




*(IV)*

[0178] wherein:

[0179] X is O or S;

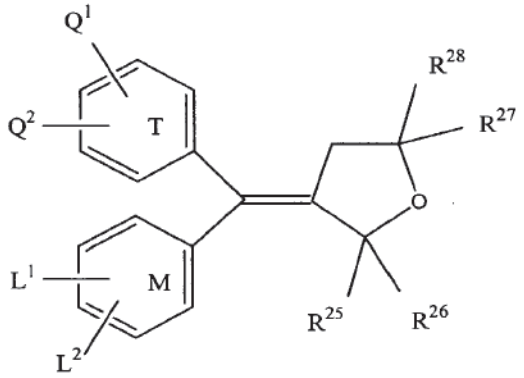
[0180] J is a carbocycle or a heterocycle;

[0181] $R^{22}$ is $NHSO_2CH_3$ or F;

[0182] $R^{23}$ is H, $NO_2$, or F; and

[0183] $R^{24}$ is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

[0184] According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula *(V)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:




*(V)*

[0185] wherein:

[0186] T and M are independently phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0187] $R^{25}$, $R^{26}$, $R^{27}$, and $R^{28}$ are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or

[0188] $R^{25}$ and $R^{26}$, together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or

[0189] $R^{27}$and $R^{28}$, together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0190] $Q^1$, $Q^2$, $L^1$ or $L^2$ are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, lower methoxy having from 1 to 6 carbon atoms, alkylsulfinyl or alkylsulfonyl; and

[0191] at least one of $Q^1$, $Q^2$, $L^1$ or $L^2$ is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or $Q^1$ and $Q^2$ together form methylenedioxy; or $L^1$ and $L^2$ together form methylenedioxy.

[0192] In another embodiment, the compounds N-(2-cyclohexyloxynitrophenyl) methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof having the structure of Formula *(V)* are employed as cyclooxygenase-2 selective inhibitors.

[0193] In a further embodiment, compounds that are useful for the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof used in connection with the method(s) of the present invention, the structures for which are set forth in Table 3 below, include, but are not limited to:

[0194] 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

[0195] 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

[0196] 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

[0197] 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

[0198] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

[0199] 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

[0200] 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

[0201] 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

[0202] 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

[0203] 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

[0204] 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);

[0205] 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);

[0206] 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);

[0207] 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);

[0208] 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);

[0209] 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);

[0210] 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);

[0211] 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);

[0212] 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);

[0213] 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);

[0214] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);

[0215] 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)

[0216] 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);

[0217] 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);

[0218] 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);

[0219] 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);

[0220] 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);

[0221] 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

[0222] 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

[0223] 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

[0224] 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

[0225] 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

[0226] 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

[0227] 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

[0228] 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

[0229] 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

[0230] 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

[0231] 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

[0232] 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

[0233] 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

[0234] 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

[0235] 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

[0236] 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

[0237] 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

[0238] 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

[0239] 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

[0240] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

[0241] 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

[0242] 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a) pyridine (B-75);

[0243] 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

[0244] 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

[0245] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

[0246] 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-79);

[0247] 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-80);

[0248] 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (B-81);

[0249] 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-82);

[0250] 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-83);

[0251] 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-84);

[0252] 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-85);

[0253] 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

[0254] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-87);

[0255] 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-88);

[0256] 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-89);

[0257] 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-90);

[0258] 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-91);

[0259] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-92);

[0260] 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-93);

[0261] 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-94);

[0262] 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl] benzenesulfonamide (B-95);

[0263] 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-96);

[0264] 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-97);

[0265] 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-98);

[0266] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-99);

[0267] 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);

[0268] 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-101);

[0269] 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-102);

[0270] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-

[0271] 5-ene (B-103);

[0272] 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-104);

[0273] 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-

[0274] 6-ene (B-105);

[0275] 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl) phenyl]spiro [2.4]hept-5-ene (B-106);

[0276] 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-107);

[0277] 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro [2.4]hept-5-ene (B-108);

[0278] 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene (B-109);

[0279] 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-110);

[0280] 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-111);

[0281] 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-112);

[0282] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

[0283] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

[0284] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

[0285] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

[0286] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino) thiazole (B-117);

[0287] 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methyl sulfonyl)phenyl]thiazole (B-118);

[0288] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

[0289] 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

[0290] 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide (B-121);

[0291] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

[0292] 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl] benzenesulfonamide (B-123);

[0293] 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

[0294] 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

[0295] 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

[0296] 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-127);

[0297] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-128);

[0298] 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-129);

[0299] 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl] pyridine (B-130);

[0300] 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-

[0301] 2-yl]pyridine (B-131);

[0302] 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

[0303] 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

[0304] 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-134);

[0305] 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

[0306] 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-136);

[0307] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

[0308] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

[0309] 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

[0310] 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoro methyl)-1H-imidazole (B-140);

[0311] 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

[0312] 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

[0313] 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-143);

[0314] 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoro methyl)-1H-imidazole (B-144);

[0315] 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

[0316] 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

[0317] 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzene sulfonamide (B-147);

[0318] 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

[0319] 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-149);

[0320] 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-150);

[0321] 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-151);

[0322] 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoro methyl)-1H-pyrazole (B-152);

[0323] 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide (B-153);

[0324] N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

[0325] ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

[0326] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

[0327] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

[0328] 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

[0329] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

[0330] 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

[0331] 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

[0332] 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

[0333] 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

[0334] 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

[0335] 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

[0336] 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

[0337] 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

[0338] 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

[0339] 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

[0340] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

[0341] 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

[0342] 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-172);

[0343] 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-173);

[0344] 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-174);

[0345] 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-175);

[0346] 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-176);

[0347] 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methyl sulfonyl)benzene (B-177);

[0348] 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-178);

[0349] 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-179);

[0350] 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-180);

[0351] 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-181);

[0352] 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);

[0353] 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);

[0354] 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-184);

[0355] 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-185);

[0356] 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl] benzenesulfonamide (B-186);

[0357] 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-187);

[0358] 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl] benzenesulfonamide (B-188);

[0359] 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);

[0360] ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);

[0361] 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl] acetic acid (B-191);

[0362] 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] oxazole (B-192);

[0363] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);

[0364] 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);

[0365] 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-195);

[0366] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);

[0367] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);

[0368] 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);

[0369] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

[0370] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-200);

[0371] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-201);

[0372] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

[0373] 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

[0374] 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

[0375] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-205);

[0376] 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

[0377] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[0378] [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl] benzenesulfonamide (B-208);

[0379] 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

[0380] 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-210);

[0381] [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (lumiracoxib; B-211);

[0382] N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

[0383] N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

[0384] N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, sodium salt (B-214);

[0385] N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide (B-215);

[0386] 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one (B-216);

[0387] (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] methylene]-4(5H)-thiazolone (B-217);

[0388] CS-502 (B-218);

[0389] LAS-34475 (B-219);

[0390] LAS-34555 (B-220);

[0391] S-33516 (B-221);

[0392] SD-8381 (B-222);

[0393] L-783003 (B-223);

[0394] N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide (B-224);

[0395] D-1367 (B-225);

[0396] L-748731 (B-226);

[0397] (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid (B-227);

[0398] CGP-28238 (B-228);

[0399] 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

[0400] GR-253035 (B-230);

[0401] 6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

[0402] S-2474 (B-232);

[0403] 4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

[0404] 4-(5-methyl-3-phenyl-4-isoxazolyl);

[0405] 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

[0406] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

[0407] N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

[0408] 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-

[0409] 1-yl]benzenesulfonamide;

[0410] (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

[0411] 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl sulfonyl)phenyl]-3(2H)-pyridzainone;

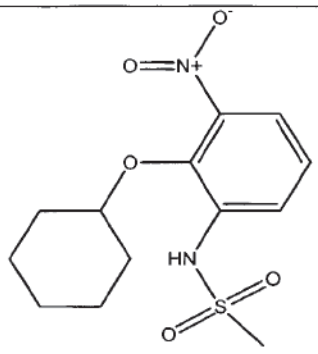
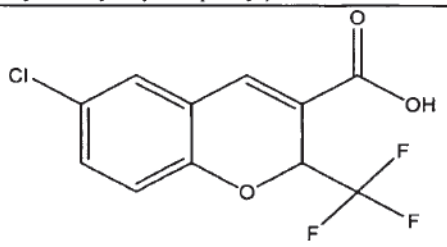
[0412] 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

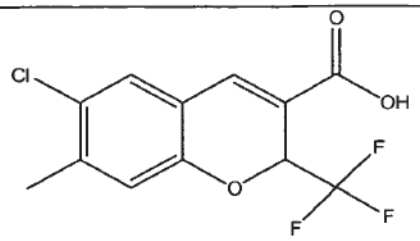
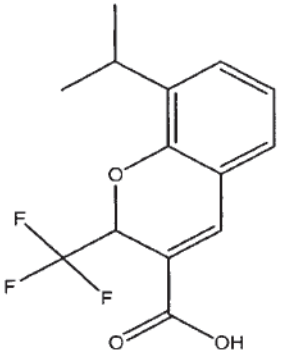
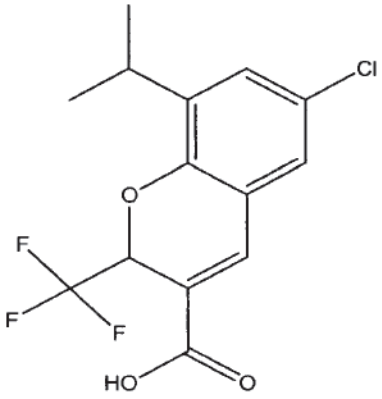
[0413] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

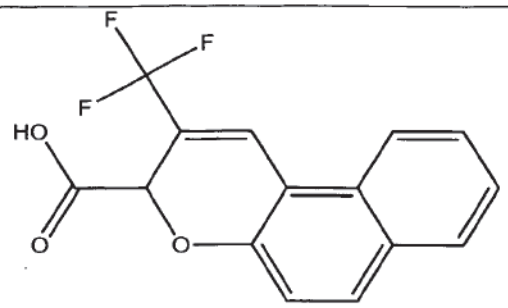
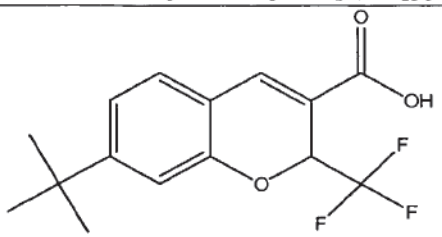
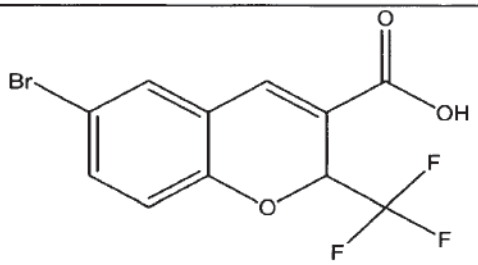
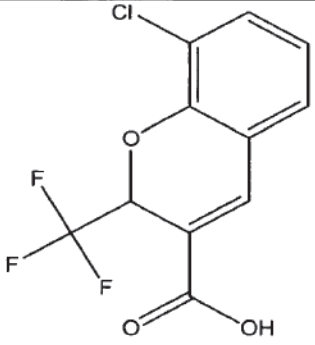
[0414] [2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid.

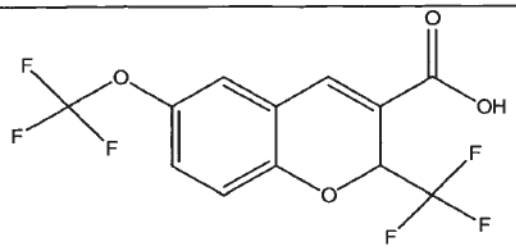
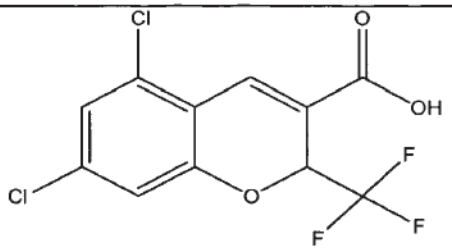
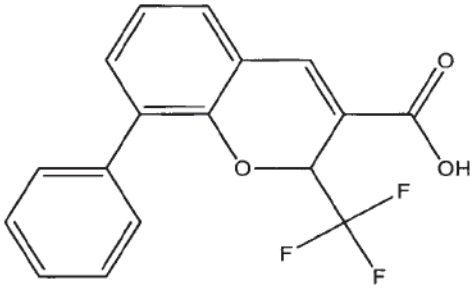
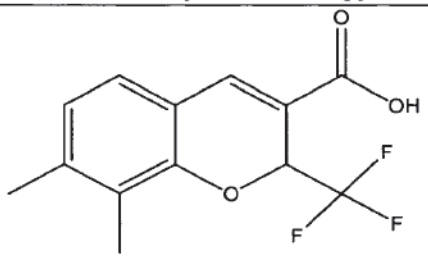
TABLE 3

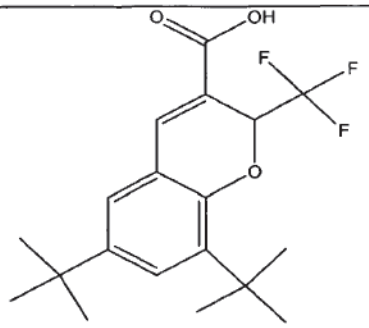
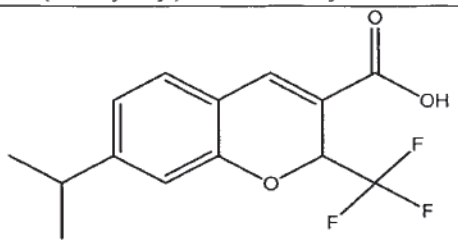
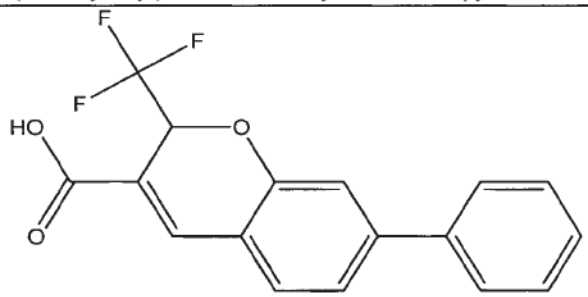
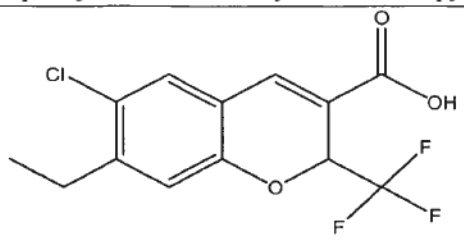
EXAMPLES OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

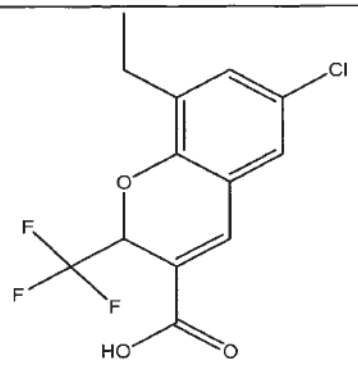
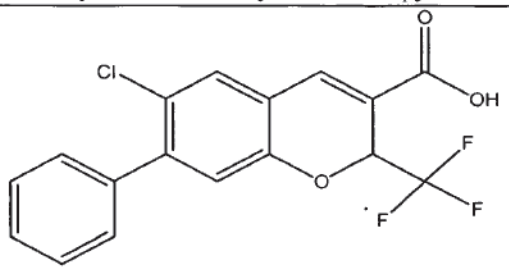
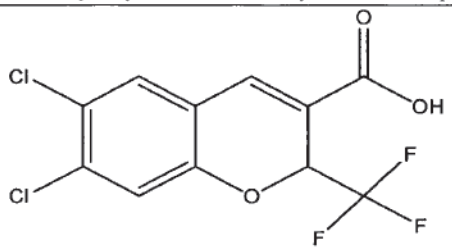
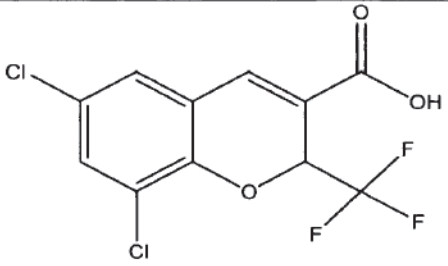
| Compound Number | Structural Formula |
|---|---|
| B-26 |  N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398; |
| B-27 |  6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

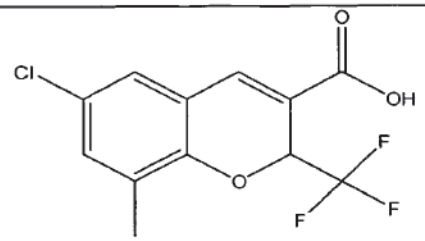
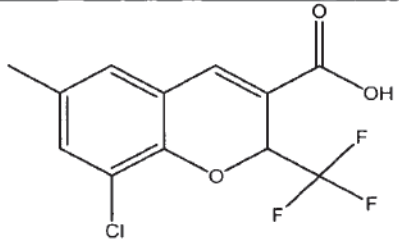
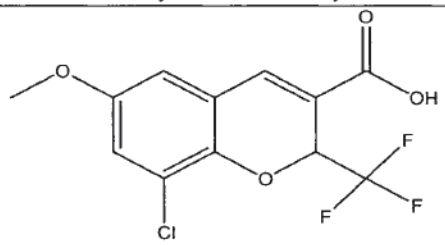
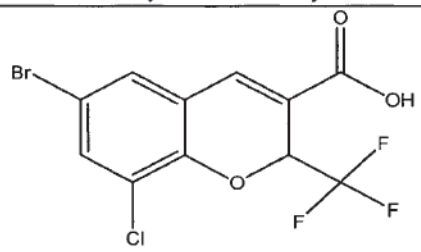
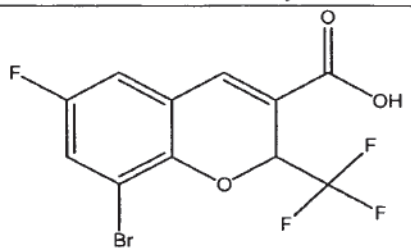
| Compound Number | Structural Formula |
|---|---|
| B-28 |  6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-29 |  8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-30 |  6-chloro-8-(1-methylethyl)-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid; |

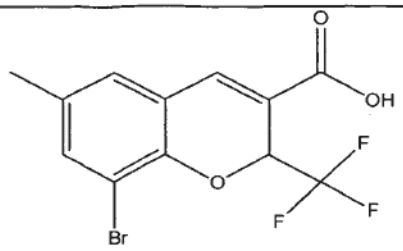
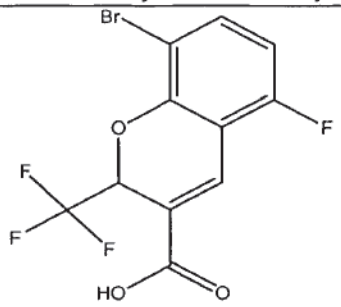
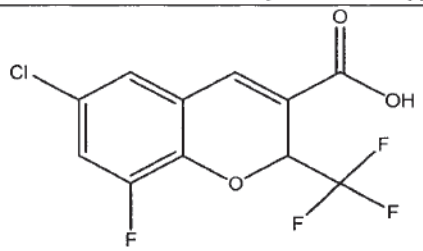
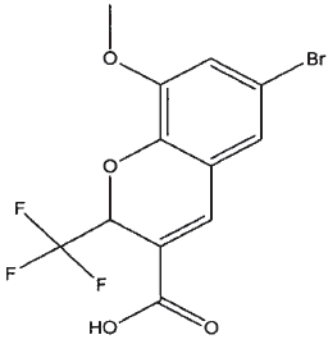
| Compound Number | Structural Formula |
|---|---|
| B-31 |  2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid; |
| B-32 |  7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-33 |  6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-34 |  8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

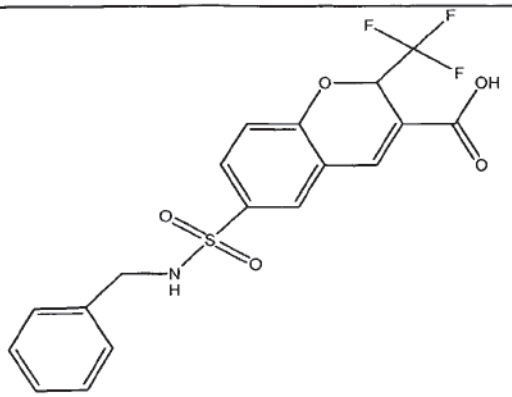
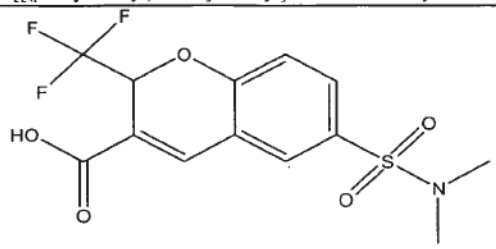
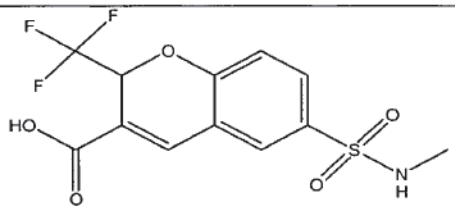
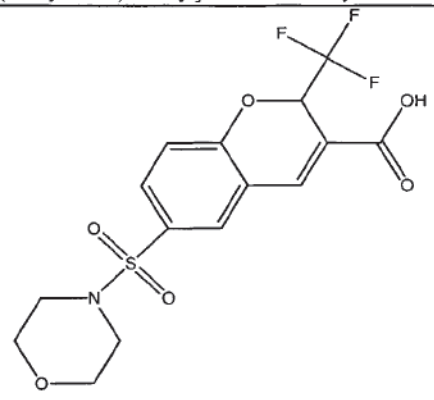
| Compound Number | Structural Formula |
|---|---|
| B-35 |  6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-36 |  5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-37 |  8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-38 |  7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

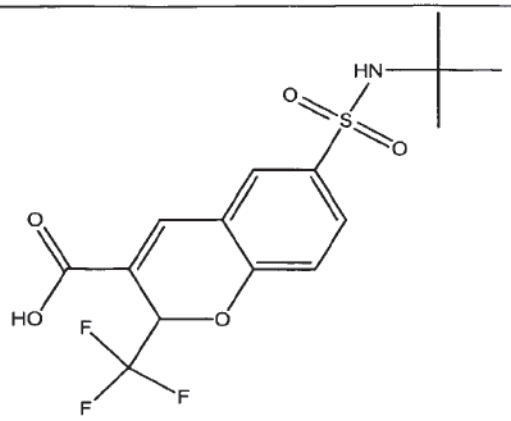
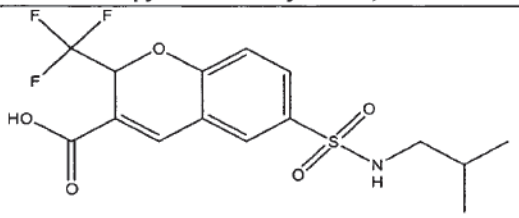
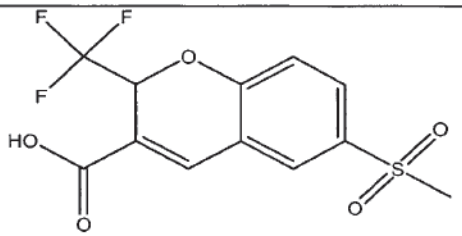
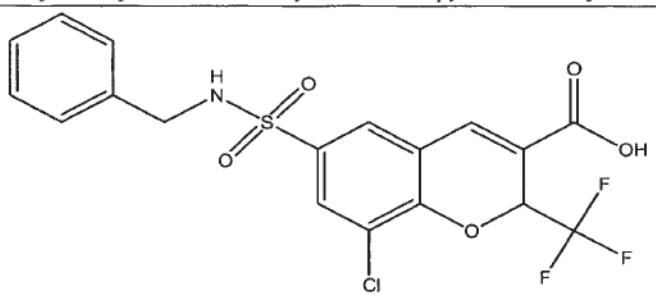
| Compound Number | Structural Formula |
|---|---|
| B-39 |  6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-40 |  7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-41 |  7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-42 |  6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

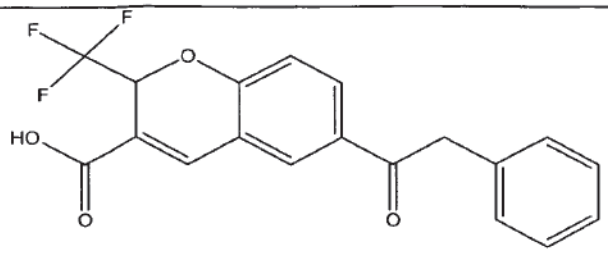
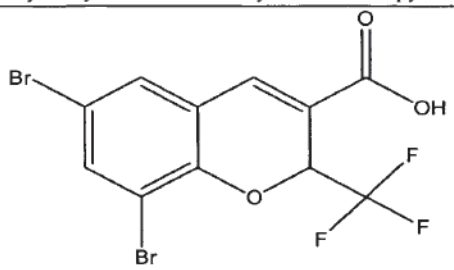
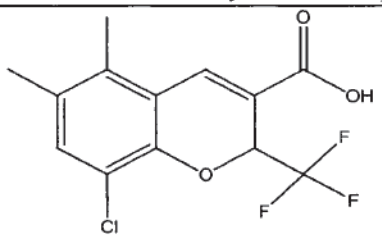
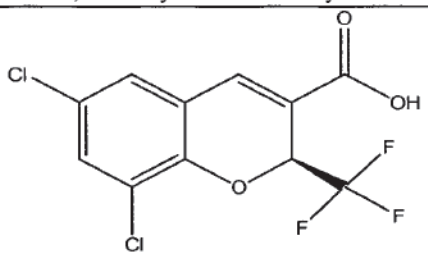
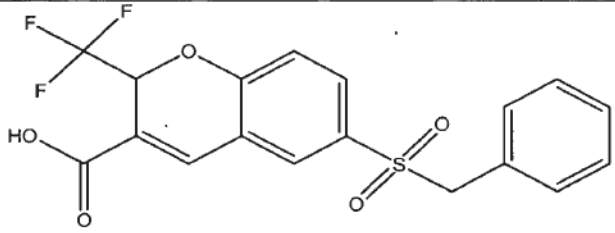
| Compound Number | Structural Formula |
|---|---|
| B-43 |  6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-44 |  6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-45 |  6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-46 |  6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

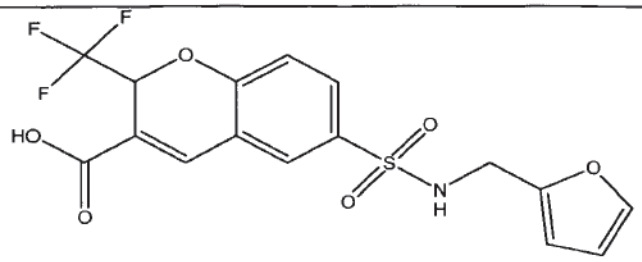
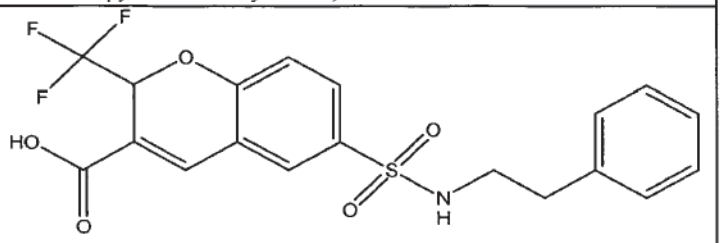
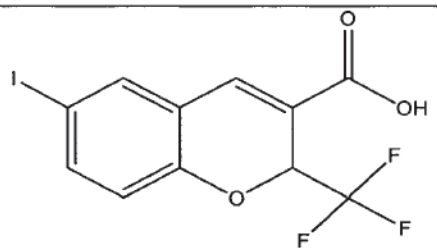
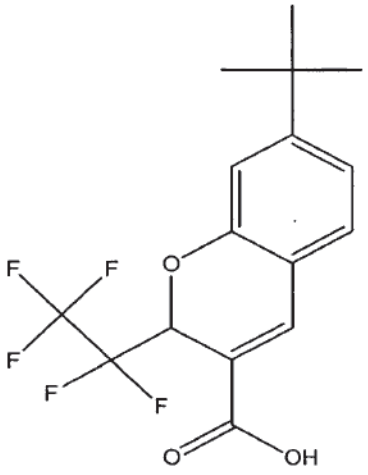
| Compound Number | Structural Formula |
|---|---|
| B-47 |  6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-48 |  8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-49 |  8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-50 |  6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-51 |  8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

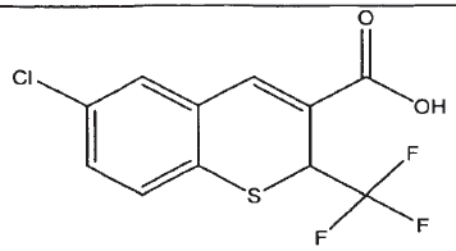
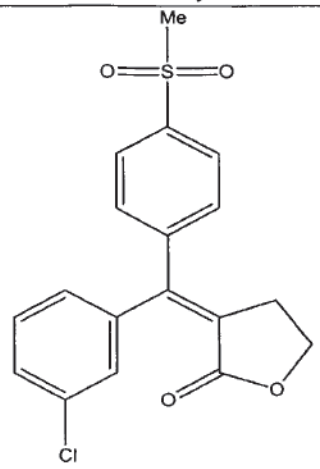
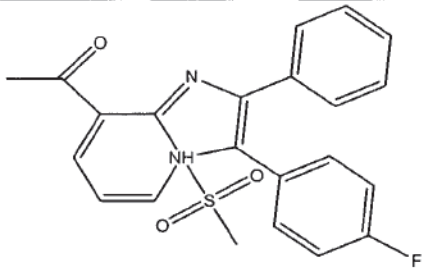
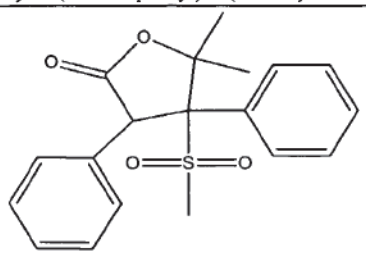
| Compound Number | Structural Formula |
|---|---|
| B-52 |  8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-53 |  8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-54 |  6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-55 |  6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

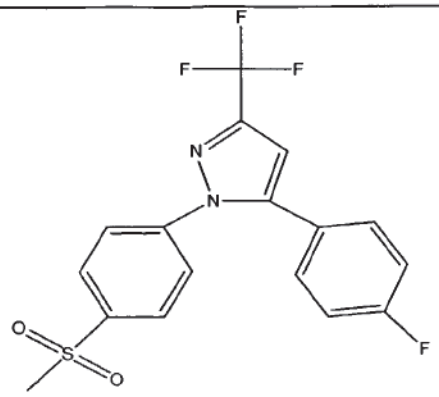
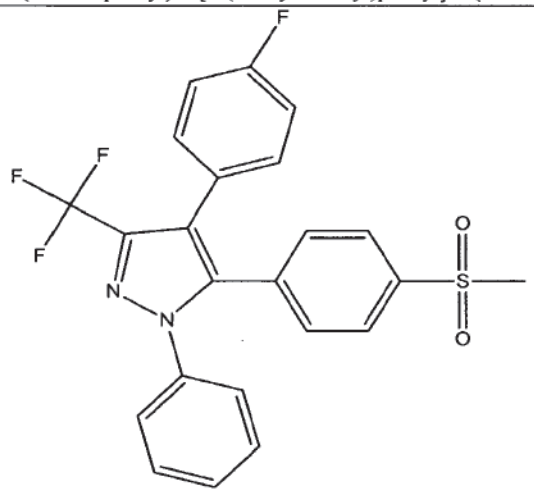
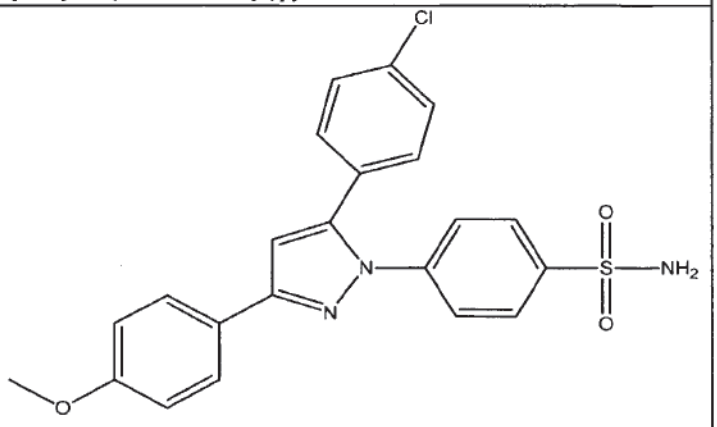
| Compound Number | Structural Formula |
|---|---|
| B-56 |  6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-57 |  6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-58 |  6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-59 |  6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

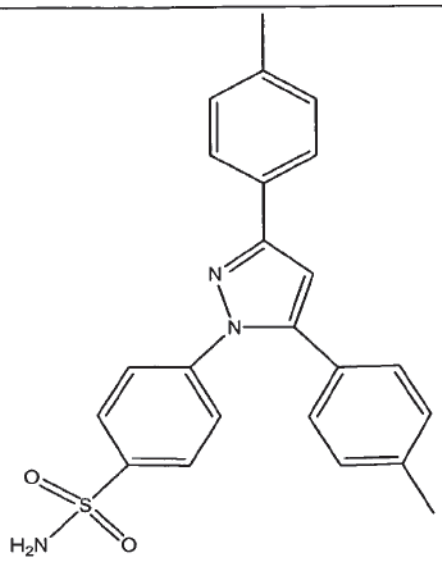
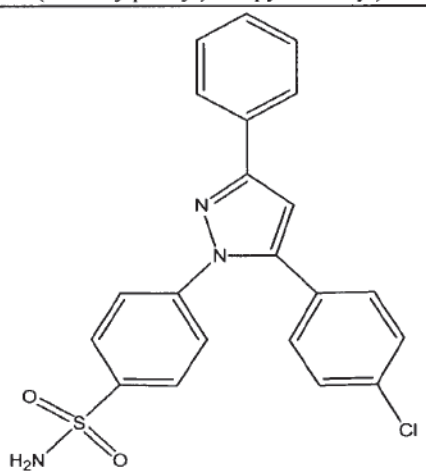
| Compound Number | Structural Formula |
|---|---|
| B-60 |  6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid; |
| B-61 |  6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-62 |  6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-63 |  8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl- 2H-1-benzopyran-3-carboxylic acid; |

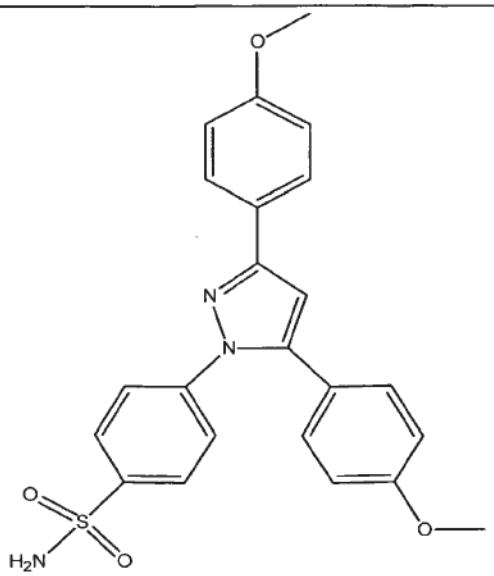
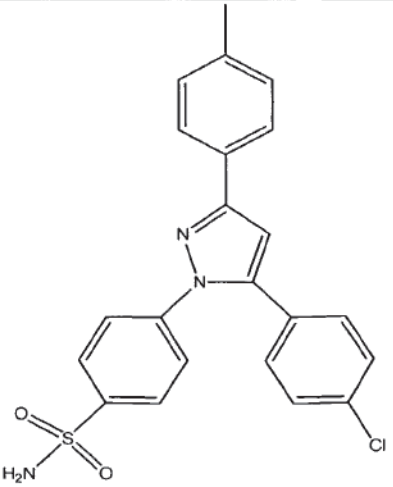
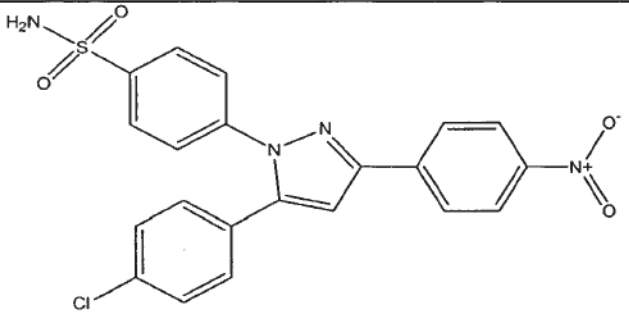
| Compound Number | Structural Formula |
|---|---|
| B-64 |  6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-65 |  6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-66 |  8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-67 |  6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-68 |  6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

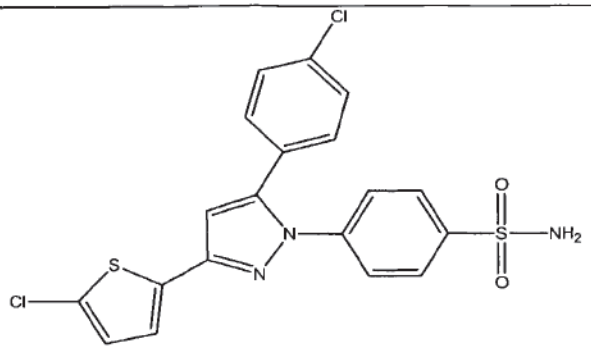
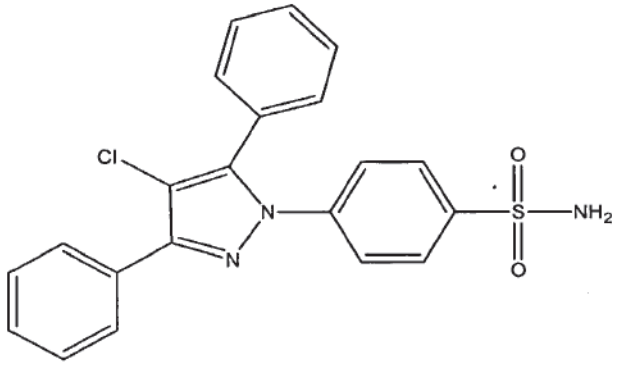
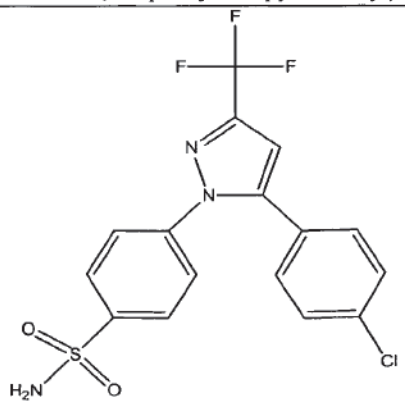
| Compound Number | Structural Formula |
|---|---|
| B-69 |  6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid; |
| B-70 |  6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran -3-carboxylic acid; |
| B-71 |  6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |
| B-72 |  7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H -1-benzopyran-3-carboxylic acid; |

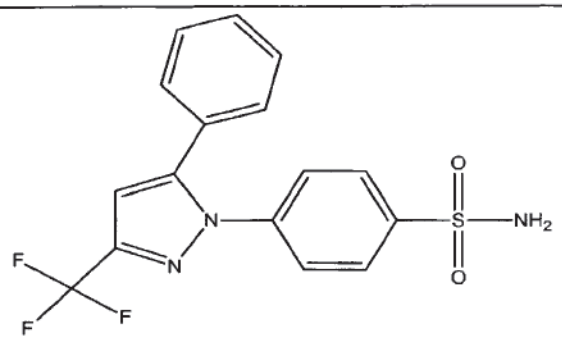
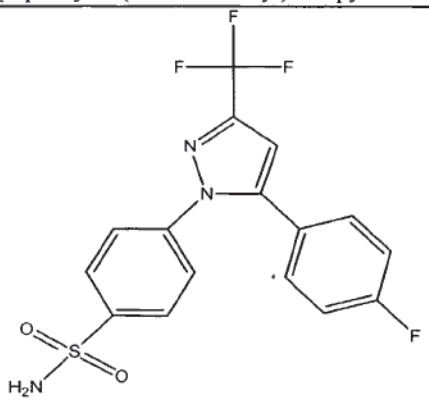
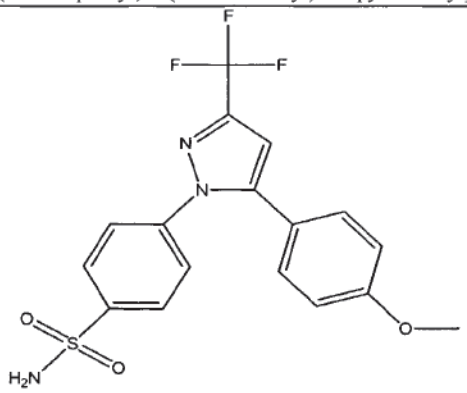
| Compound Number | Structural Formula |
|---|---|
| B-73 |  6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid; |
| B-74 |  3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene] -dihydro-furan-2-one or BMS-347070; |
| B-75 |  8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine; |
| B-76 |  5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone; |

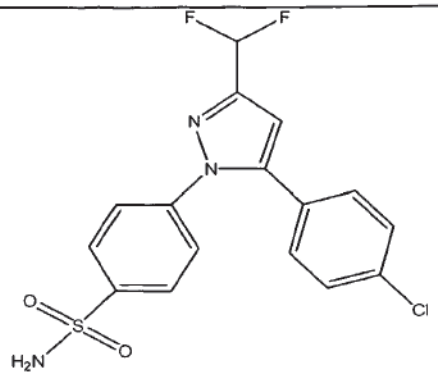
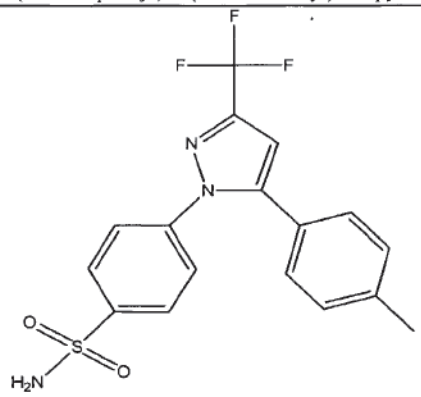
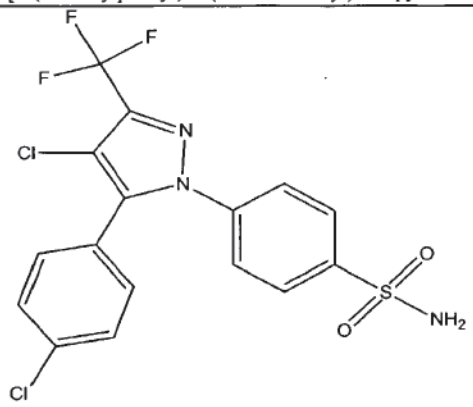
| Compound Number | Structural Formula |
|---|---|
| B-77 |  5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole; |
| B-78 |  4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -1-phenyl-3-(trifluoromethyl)pyrazole; |
| B-79 |  4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide; |

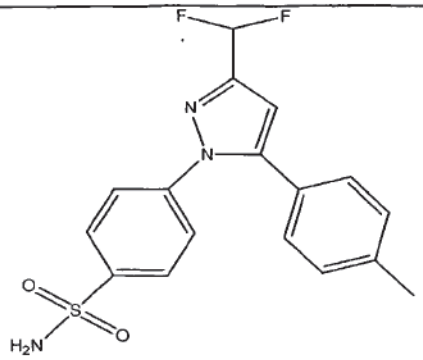
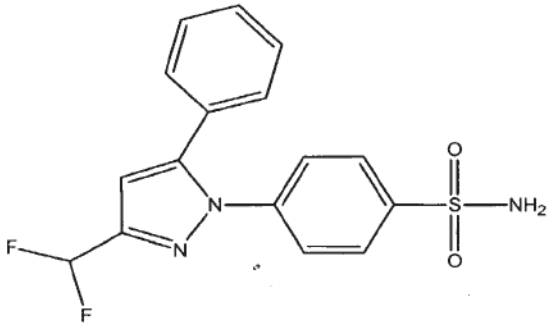
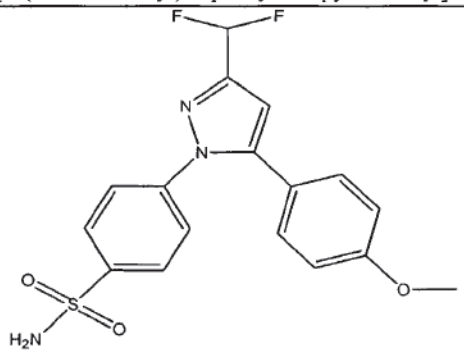
| Compound Number | Structural Formula |
|---|---|
| B-80 |  4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide; |
| B-81 |  4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide; |

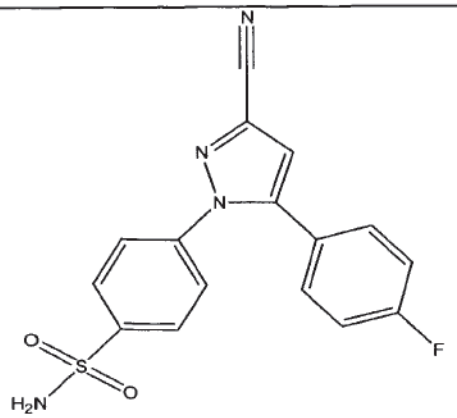
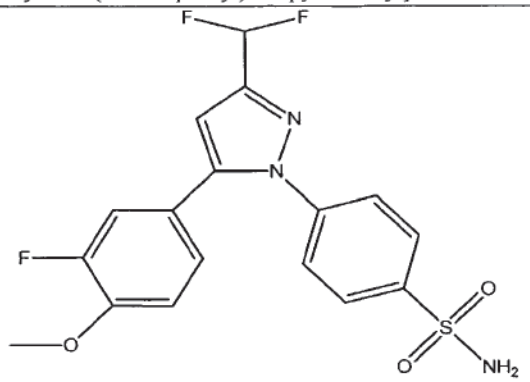
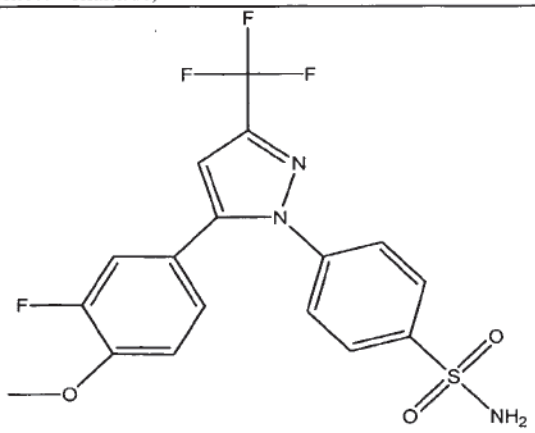
| Compound Number | Structural Formula |
|---|---|
| B-82 |  4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide; |
| B-83 |  4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide; |
| B-84 |  4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide; |

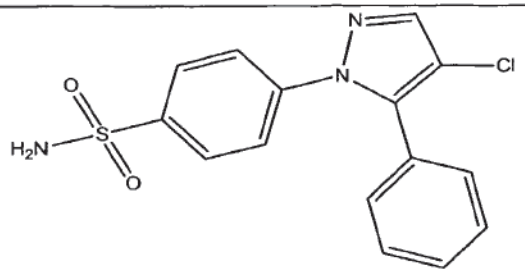
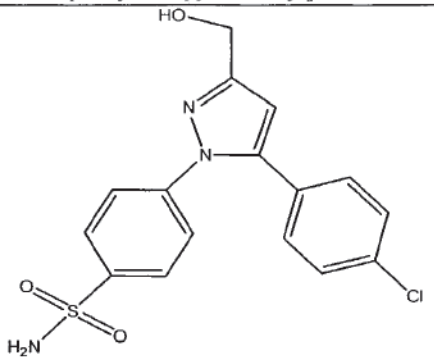
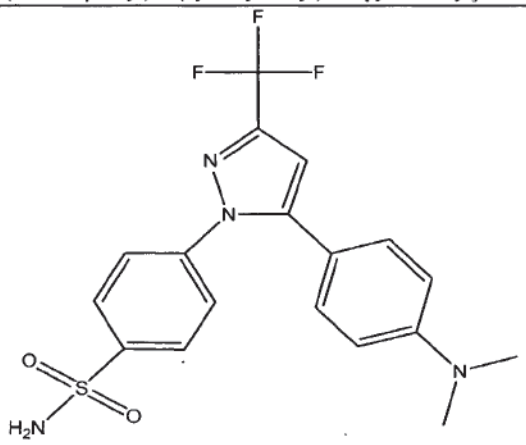
| Compound Number | Structural Formula |
|---|---|
| B-85 |  4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide; |
| B-86 |  4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide; |
| B-87 |  4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |

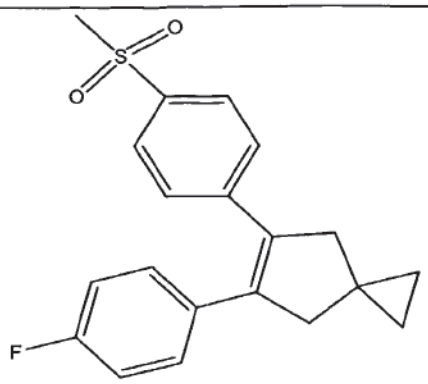
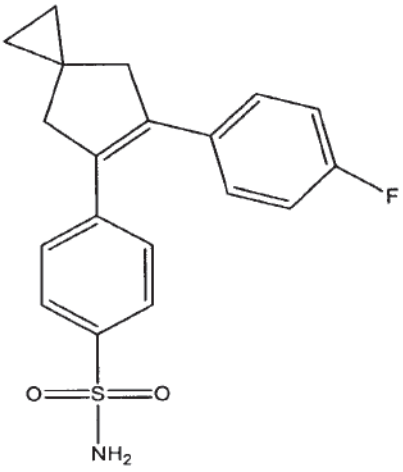
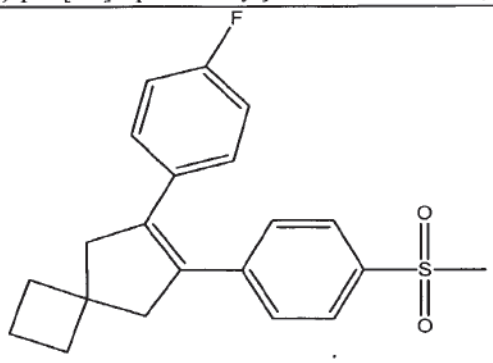
| Compound Number | Structural Formula |
|---|---|
| B-88 |  4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-89 |  4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-90 |  4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |

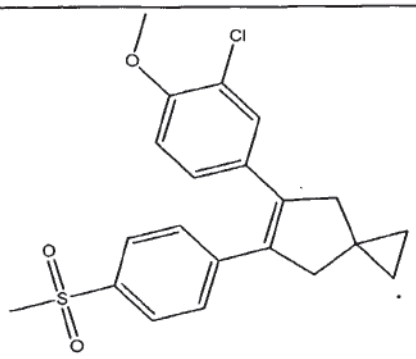
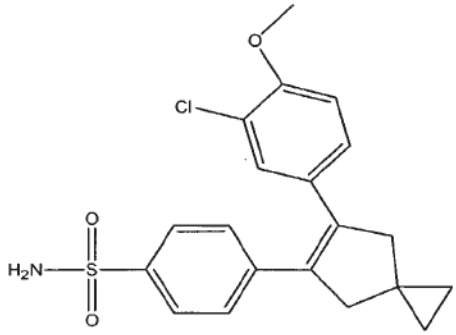
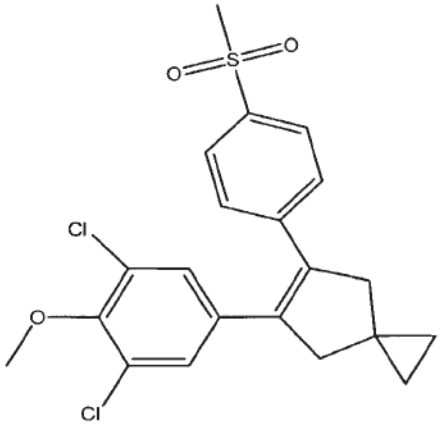
| Compound Number | Structural Formula |
|---|---|
| B-91 |  4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-92 |  4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-93 |  4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide; |

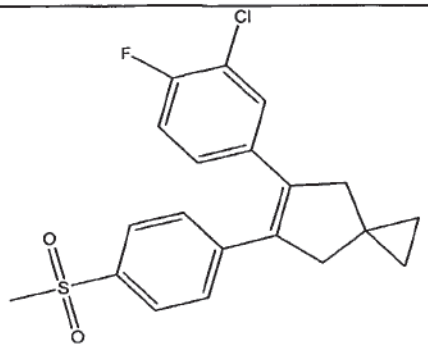
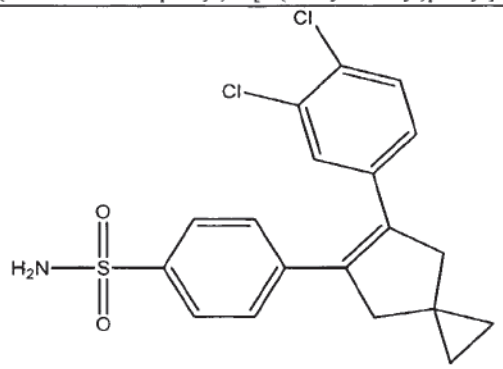
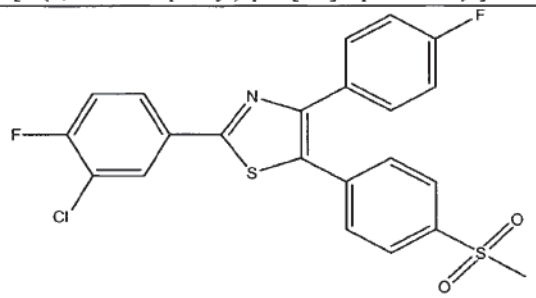
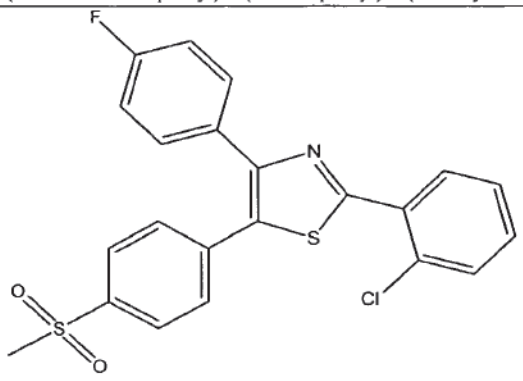
| Compound Number | Structural Formula |
|---|---|
| B-94 |  4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-95 |  4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-96 |  4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide; |

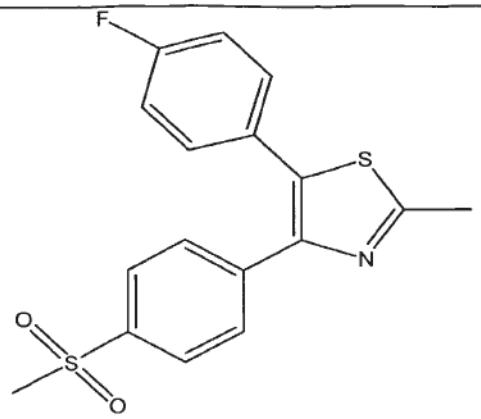
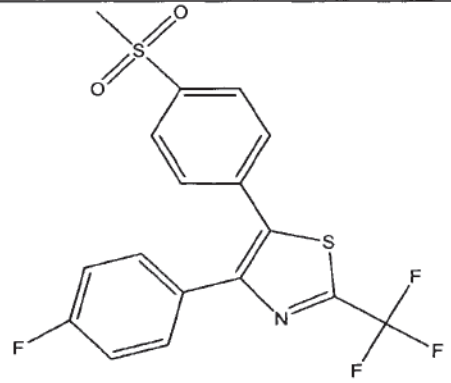
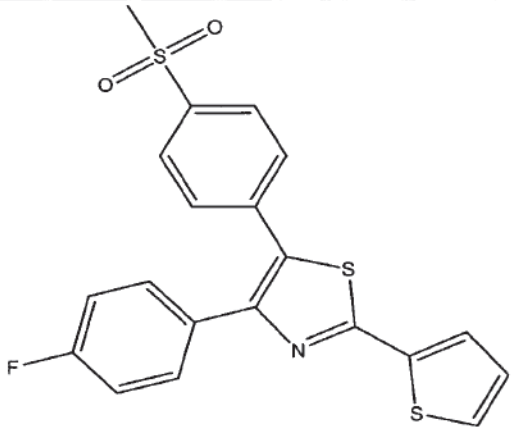
| Compound Number | Structural Formula |
|---|---|
| B-97 |  4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-98 |  4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide; |
| B-99 |  4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide; |

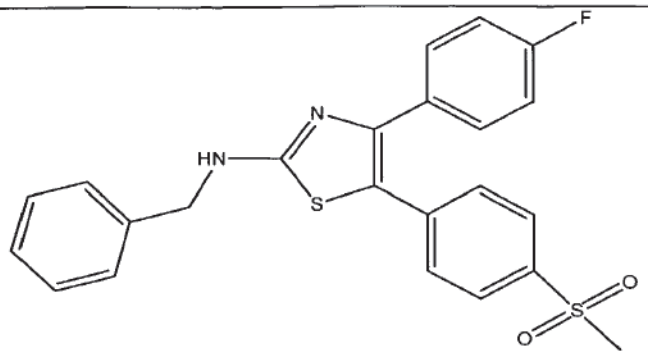
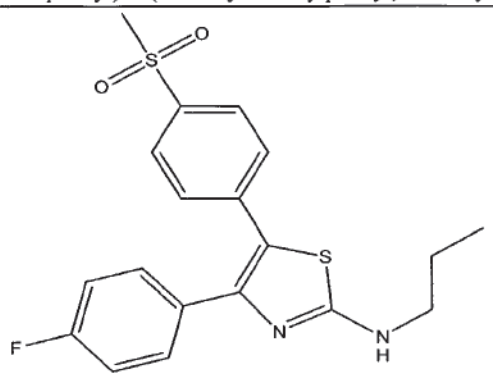
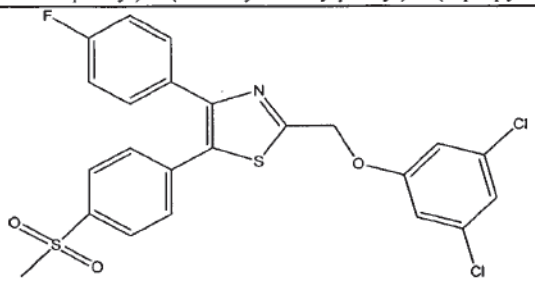
| Compound Number | Structural Formula |
|---|---|
| B-100 |  4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-101 |  4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-102 |  4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide; |

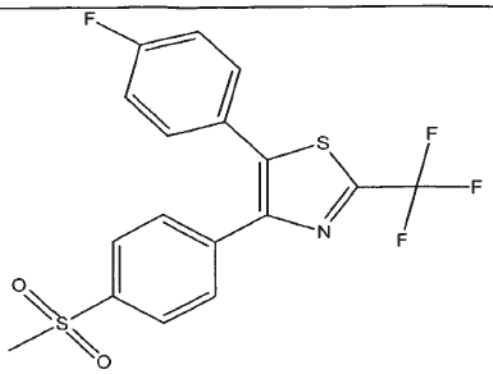
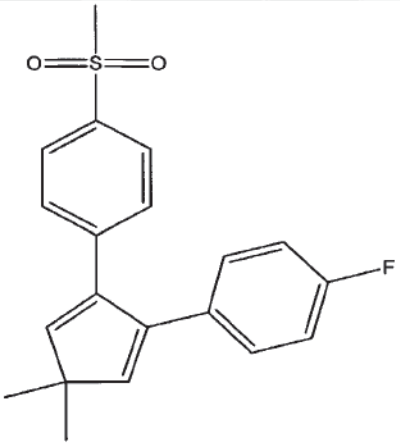
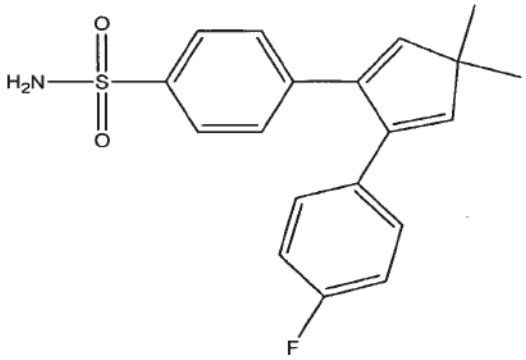
| Compound Number | Structural Formula |
|---|---|
| B-103 |  5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene; |
| B-104 |  4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide; |
| B-105 |  6-(4-fluorophenyl)-7-[4-methylsulfonyl)phenyl]spiro[3.4]oct-6-ene; |

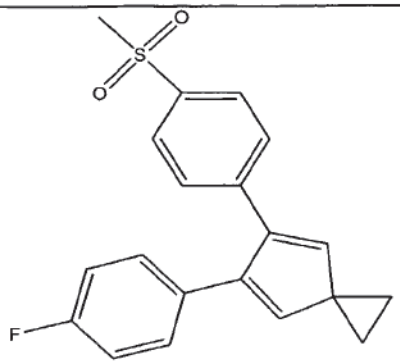
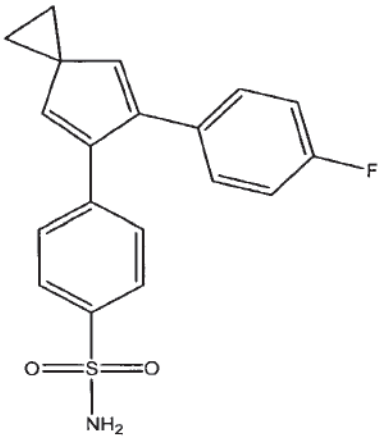
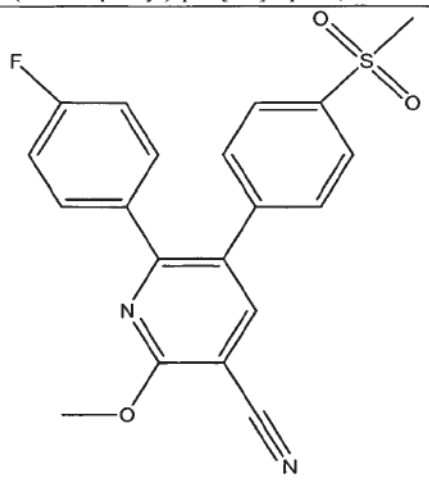
| Compound Number | Structural Formula |
|---|---|
| B-106 |  5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene; |
| B-107 |  4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide; |
| B-108 |  5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene; |

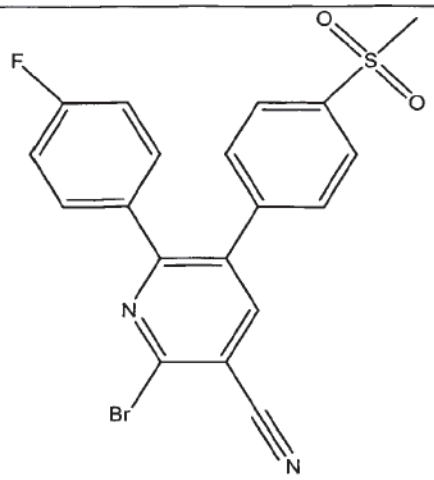
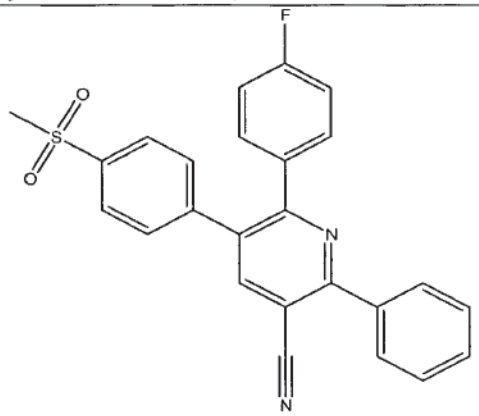
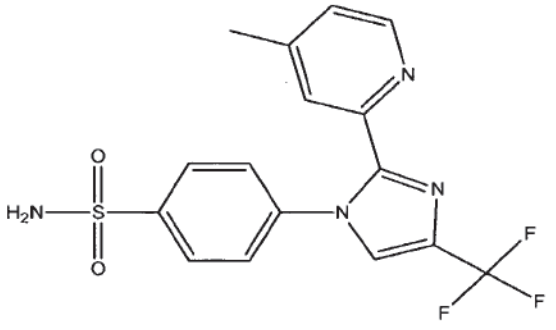
| Compound Number | Structural Formula |
|---|---|
| B-109 |  5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene; |
| B-110 |  4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide; |
| B-111 |  2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole; |
| B-112 |  2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole; |

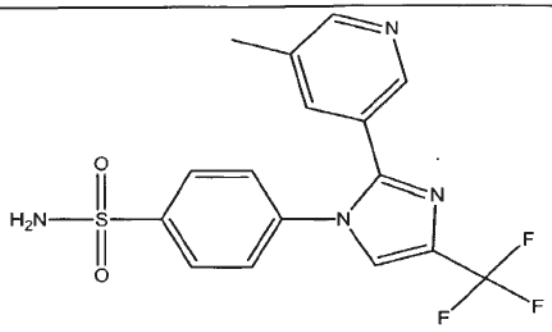
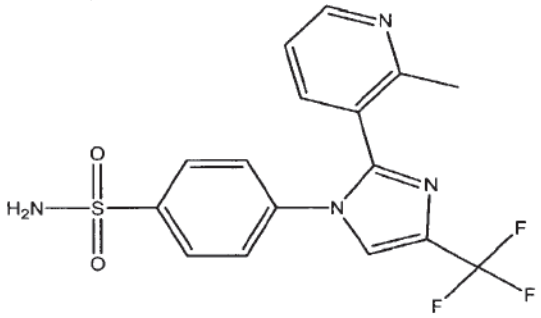
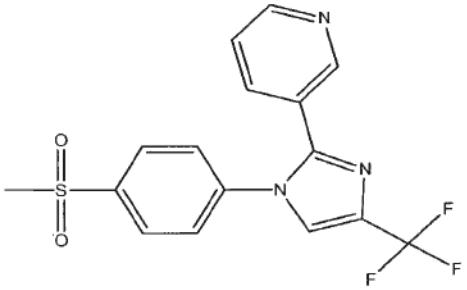
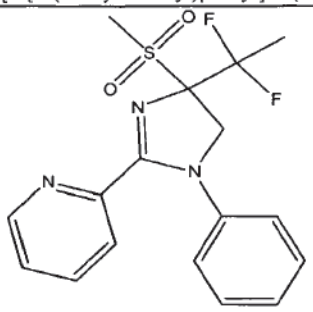
| Compound Number | Structural Formula |
|---|---|
| B-113 |  5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole; |
| B-114 |  4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole; |
| B-115 |  4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole; |

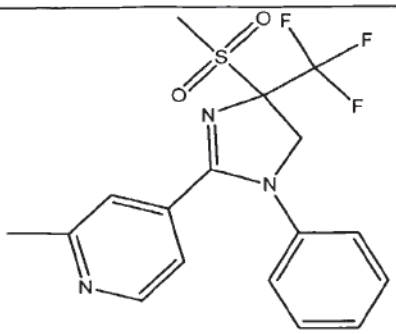
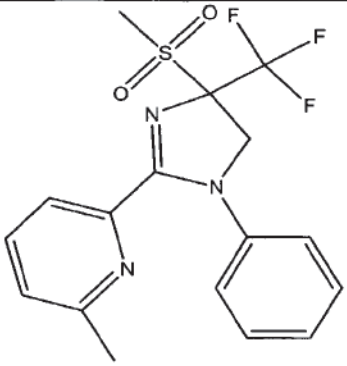
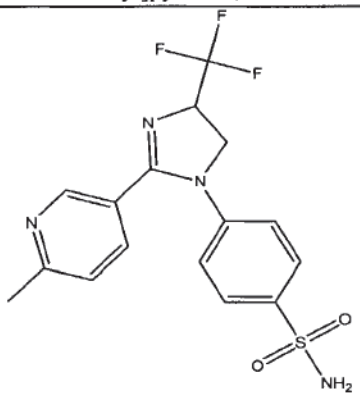
| Compound Number | Structural Formula |
|---|---|
| B-116 |  4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole; |
| B-117 |  4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole; |
| B-118 |  2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole; |

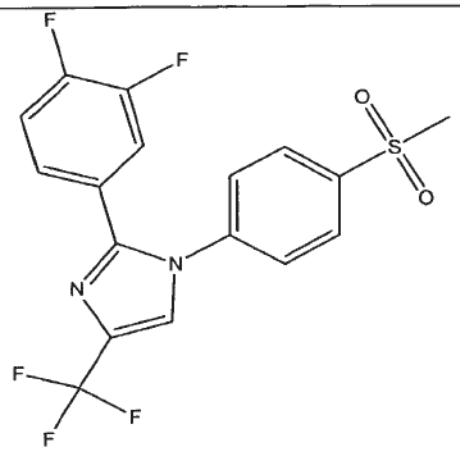
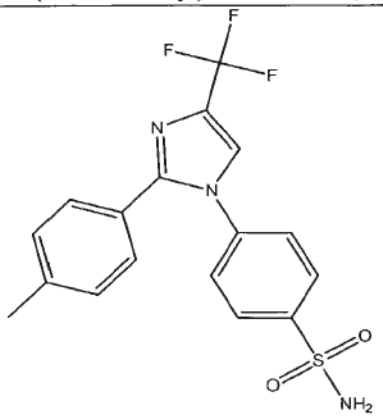
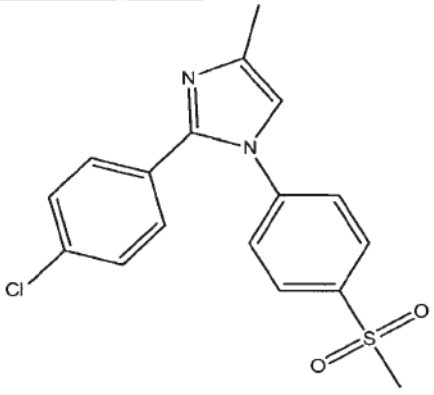
| Compound Number | Structural Formula |
|---|---|
| B-119 |  5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole; |
| B-120 |  1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl) cyclopenta-2,4-dien-3-yl]benzene; |
| B-121 |  4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide; |

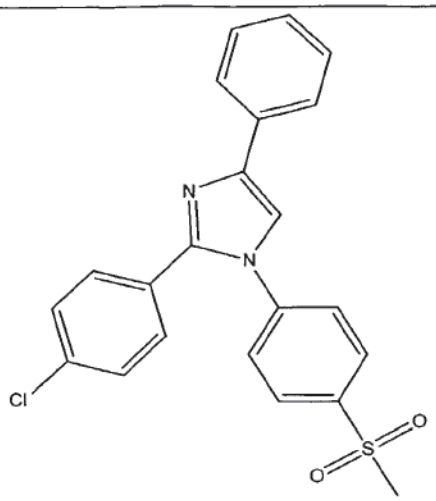
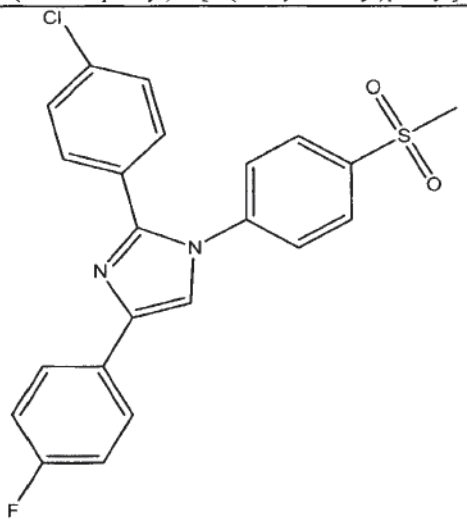
| Compound Number | Structural Formula |
|---|---|
| B-122 |  5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene; |
| B-123 |  4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide; |
| B-124 |  6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile; |

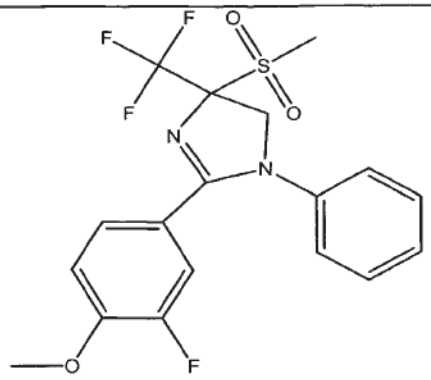
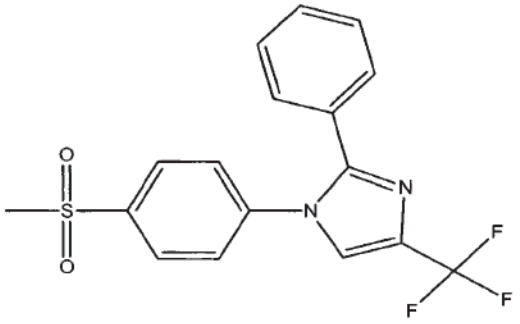
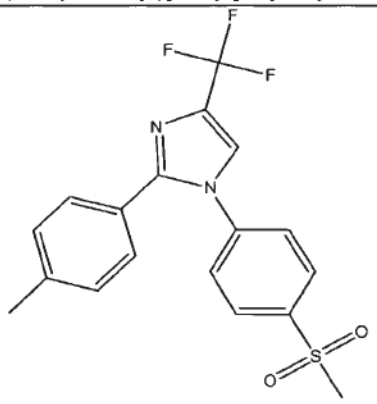
| Compound Number | Structural Formula |
|---|---|
| B-125 |  2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile; |
| B-126 |  6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile; |
| B-127 |  4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide; |

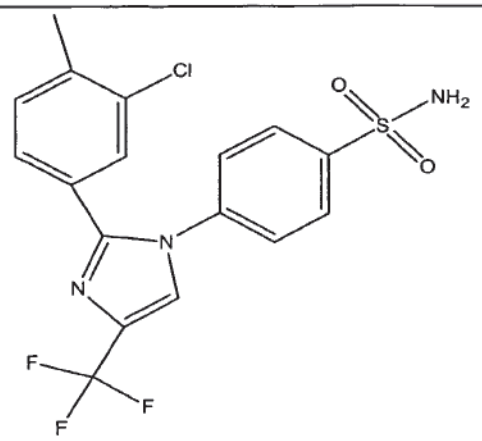
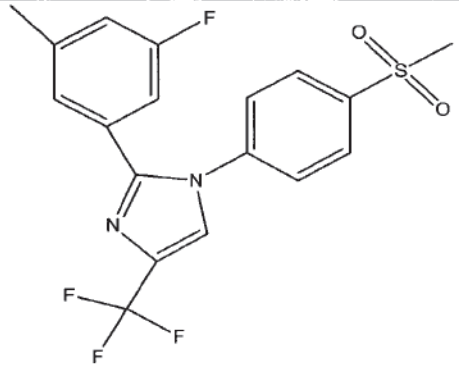
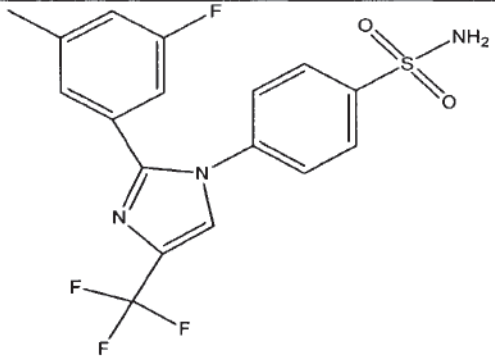
| Compound Number | Structural Formula |
|---|---|
| B-128 |  4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide; |
| B-129 |  4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide; |
| B-130 |  3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine; |
| B-131 |  2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine; |

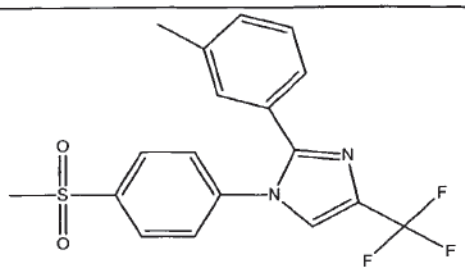
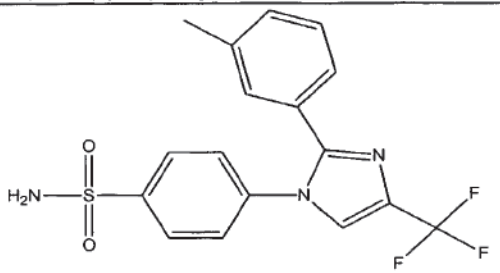
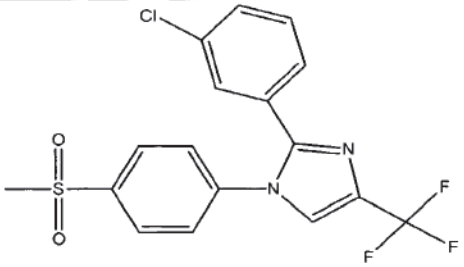
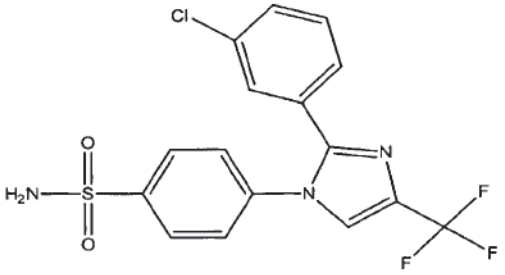
| Compound Number | Structural Formula |
|---|---|
| B-132 |  2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine; |
| B-133 |  2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine; |
| B-134 |  4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide; |

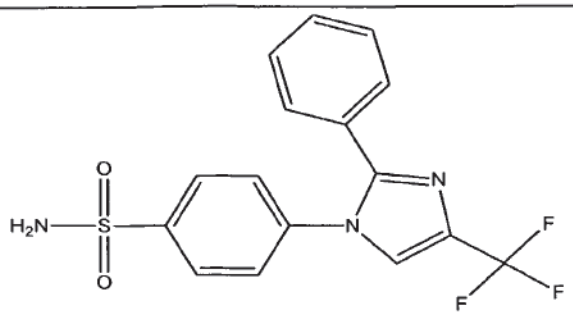
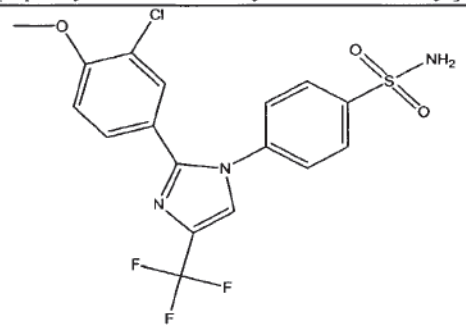
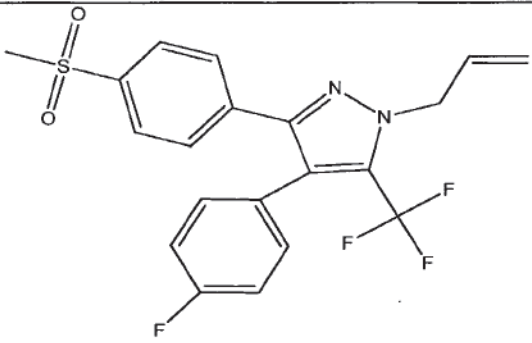
| Compound Number | Structural Formula |
|---|---|
| B-135 |  2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole; |
| B-136 |  4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide; |
| B-137 |  2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole; |

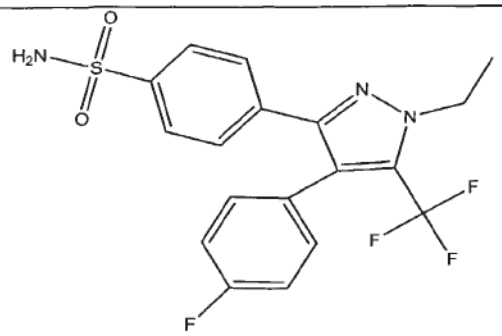
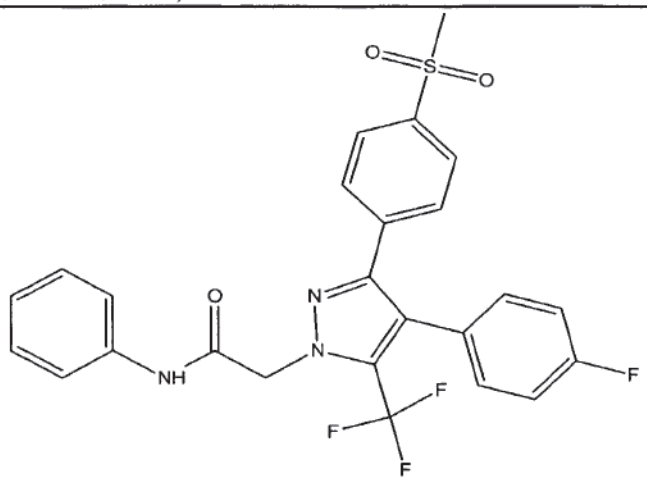
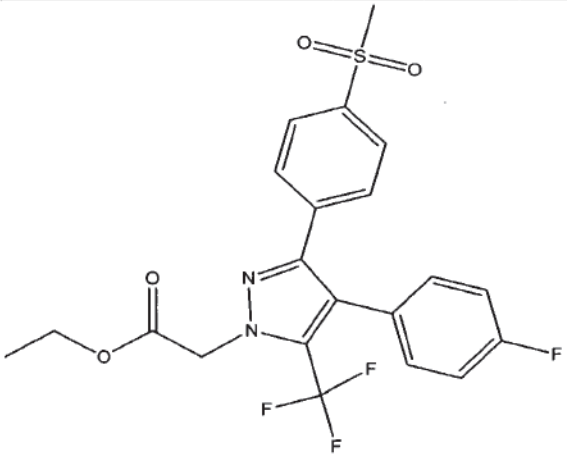
| Compound Number | Structural Formula |
|---|---|
| B-138 |  2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole; |
| B-139 |  2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl] -1H-imidazole; |

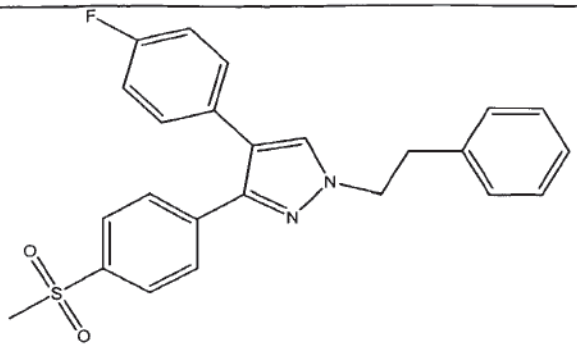
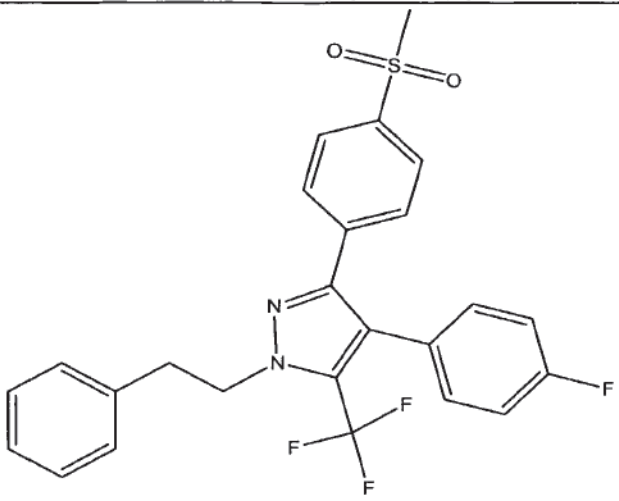
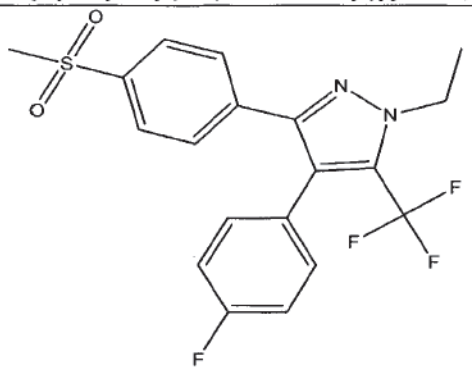
| Compound Number | Structural Formula |
|---|---|
| B-140 |  2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl -4-(trifluoromethyl)]-1H-imidazole; |
| B-141 |  1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole; |
| B-142 |  2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole; |

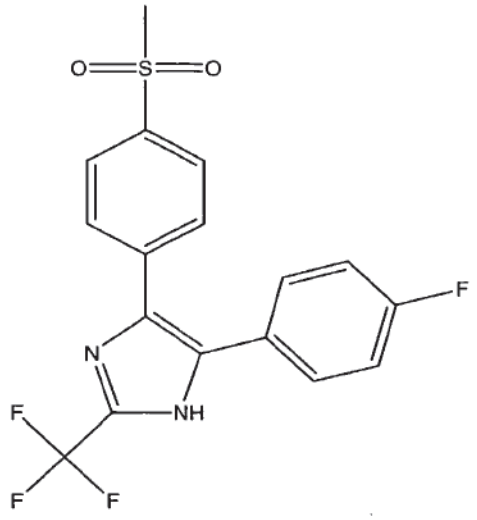
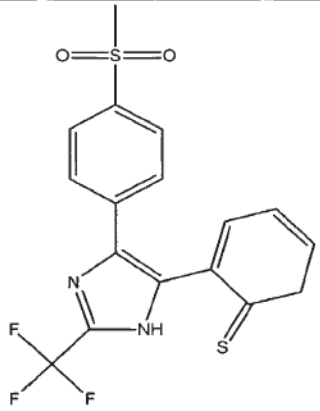
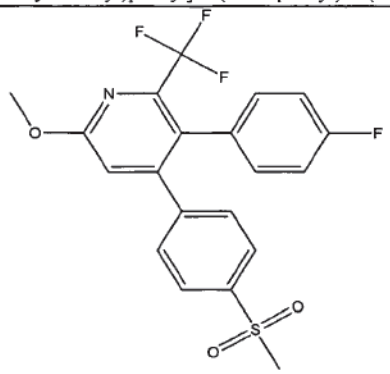
| Compound Number | Structural Formula |
|---|---|
| B-143 |  4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide; |
| B-144 |  2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole; |
| B-145 |  4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl -1H-imidazole-1-yl]benzenesulfonamide; |

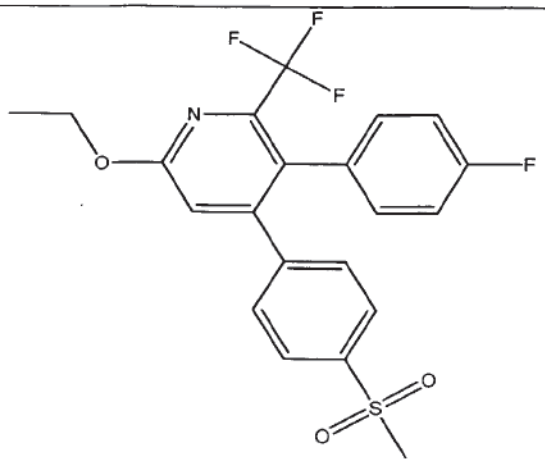
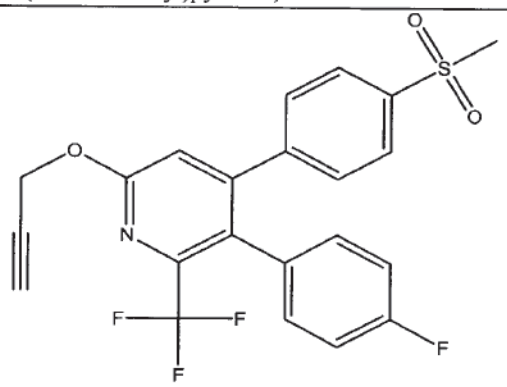
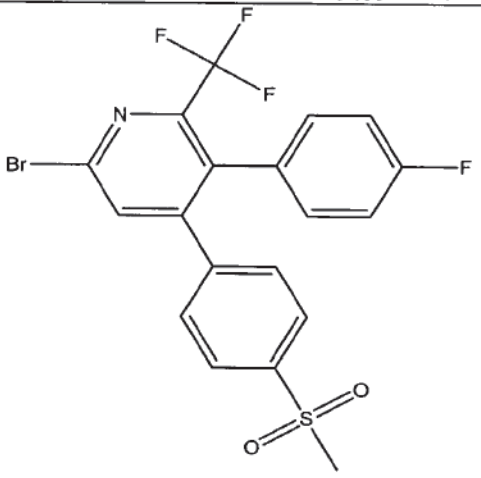
| Compound Number | Structural Formula |
|---|---|
| B-146 |  2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole; |
| B-147 |  4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide; |
| B-148 |  1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole |
| B-149 |  4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide; |

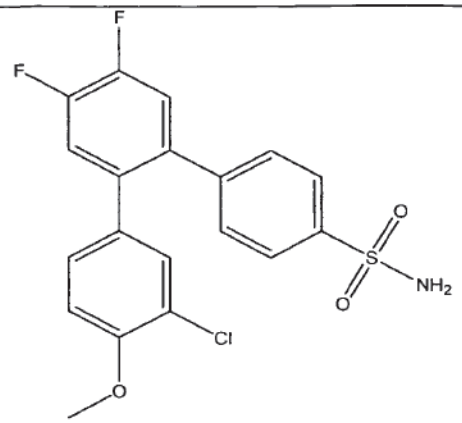
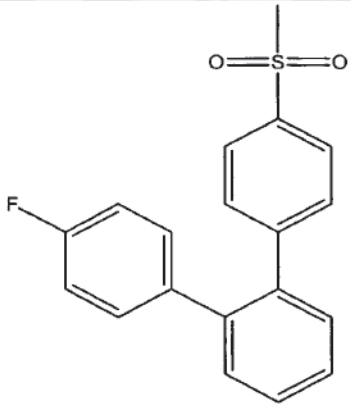
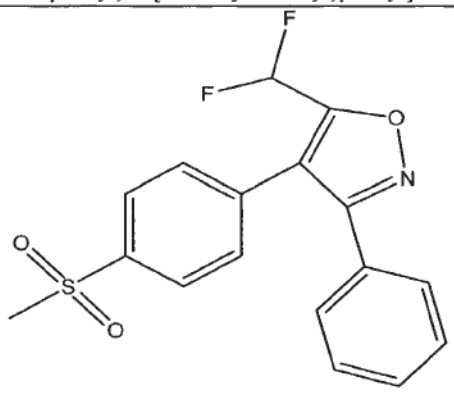
| Compound Number | Structural Formula |
|---|---|
| B-150 |  4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide; |
| B-151 |  4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide; |
| B-152 |  1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole; |

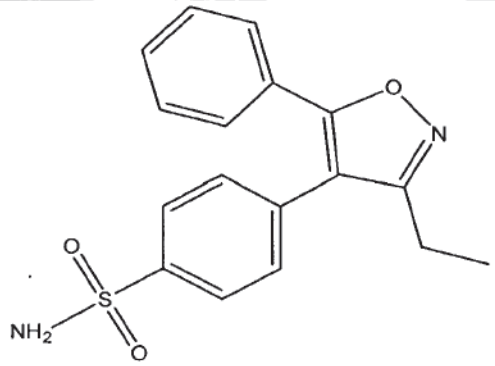
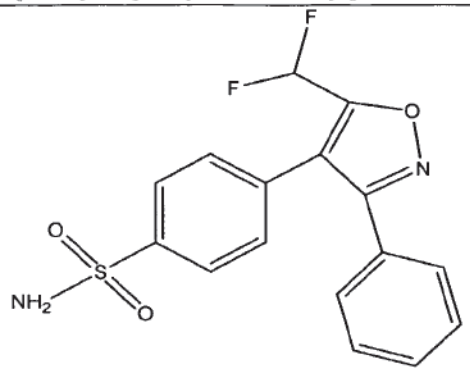
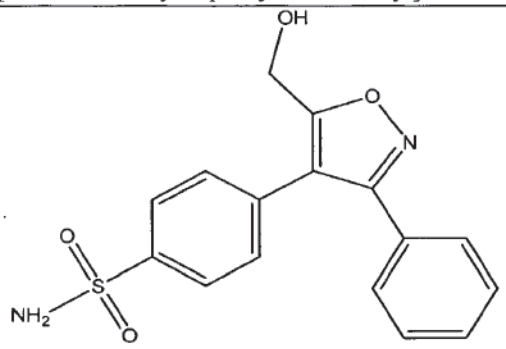
| Compound Number | Structural Formula |
|---|---|
| B-153 |  4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide; |
| B-154 |  N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide; |
| B-155 |  ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate; |

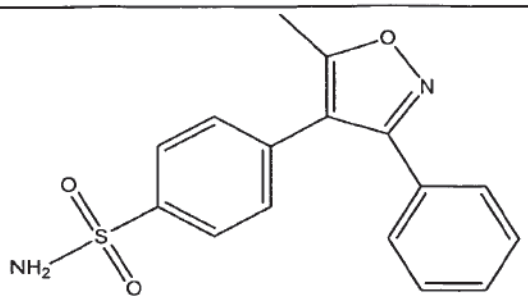
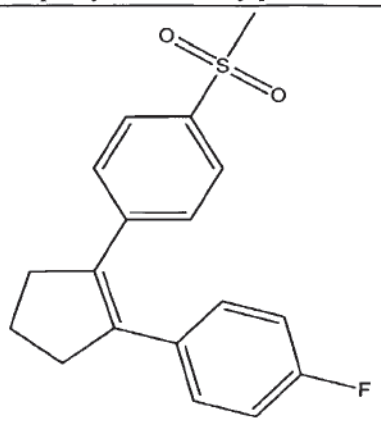
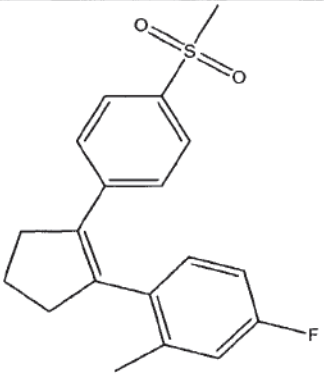
| Compound Number | Structural Formula |
|---|---|
| B-156 |  4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole; |
| B-157 |  4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole; |
| B-158 |  1-ethyl-4-(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole; |

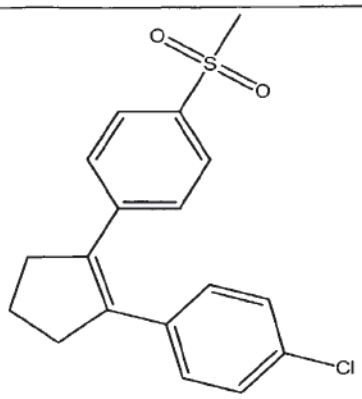
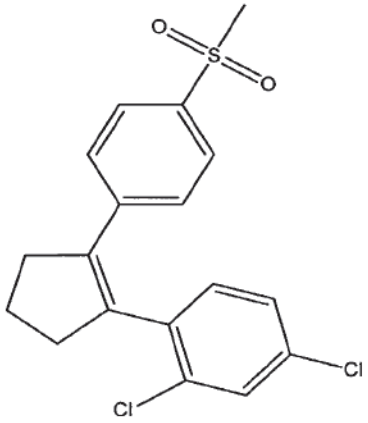
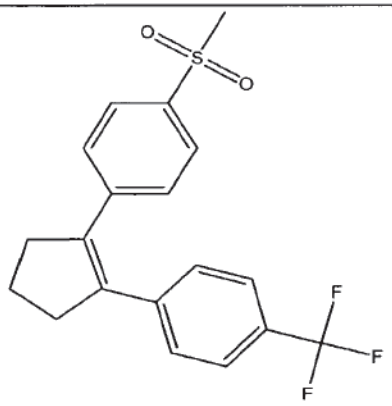
| Compound Number | Structural Formula |
|---|---|
| B-159 |  5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl) -2-trifluoromethyl-1H-imidazole; |
| B-160 |  4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole; |
| B-161 |  5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine; |

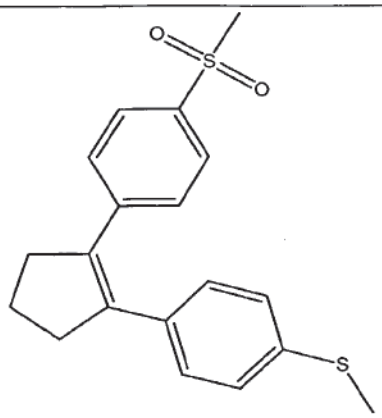
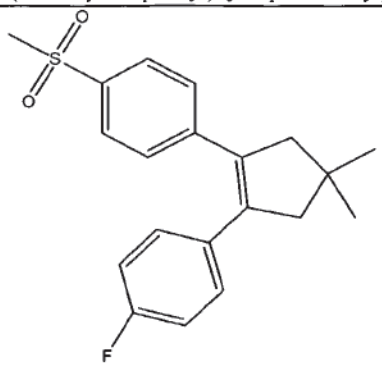
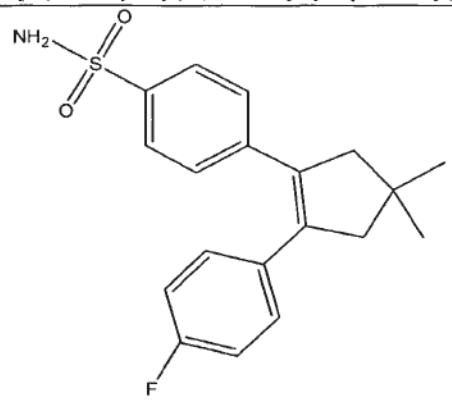
| Compound Number | Structural Formula |
|---|---|
| B-162 |  2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine; |
| B-163 |  5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -2-(2-propynyloxy)-6-(trifluoromethyl)pyridine; |
| B-164 |  2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine; |

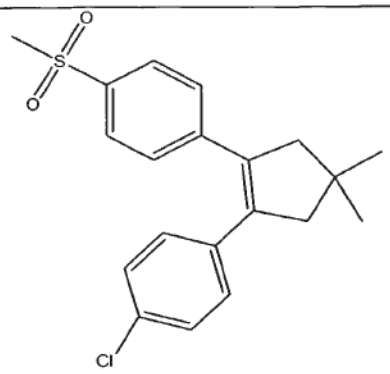
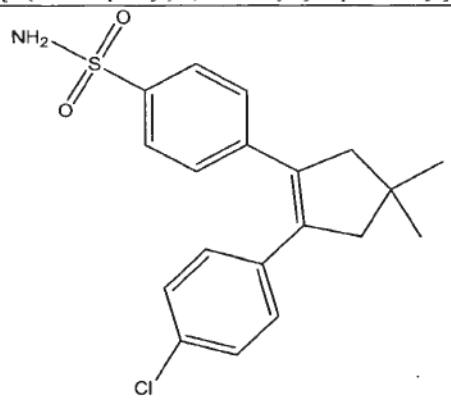
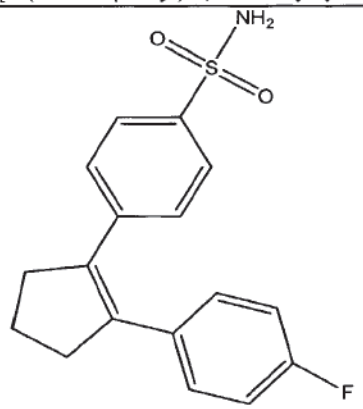
| Compound Number | Structural Formula |
|---|---|
| B-165 |  4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide; |
| B-166 |  1-(4-fluorophenyl)-2-[4-methylsulfonyl)phenyl]benzene; |
| B-167 |  5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole; |

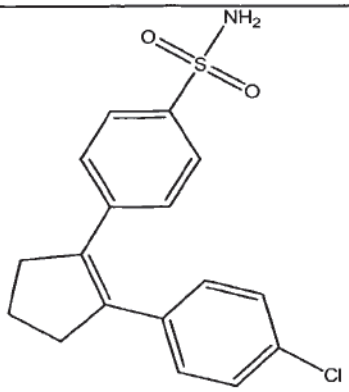
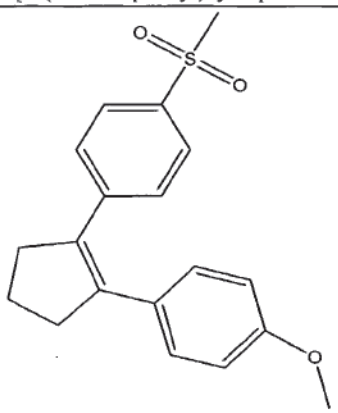
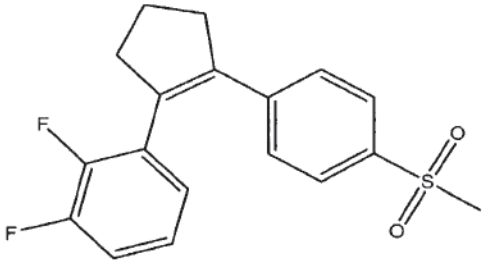
| Compound Number | Structural Formula |
|---|---|
| B-168 |  4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide; |
| B-169 |  4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide; |
| B-170 |  4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide; |

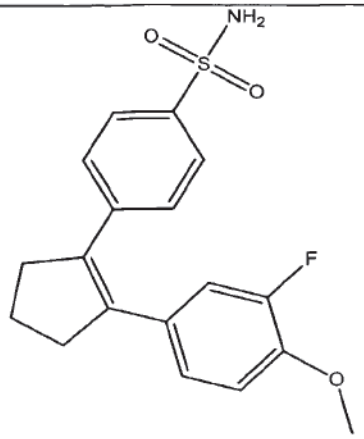
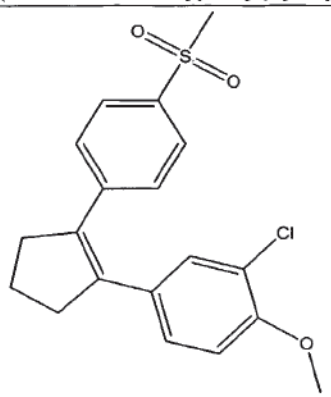
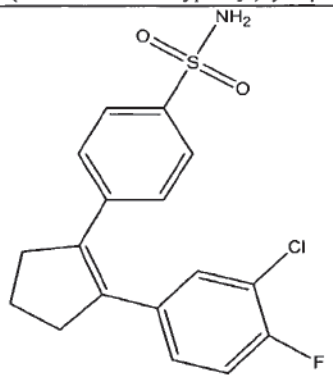
| Compound Number | Structural Formula |
|---|---|
| B-171 |  4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide; |
| B-172 |  1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-173 |  1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |

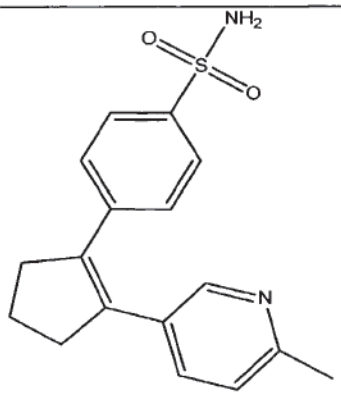
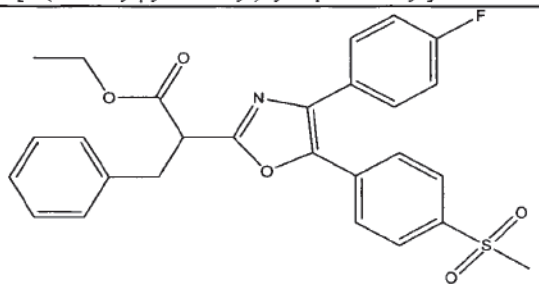
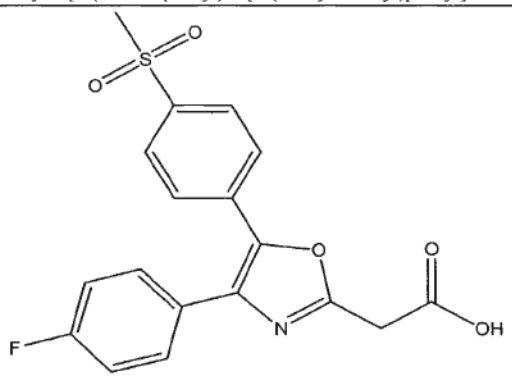
| Compound Number | Structural Formula |
|---|---|
| B-174 |  1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-175 |  1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-176 |  1-[2-(4-trifloromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |

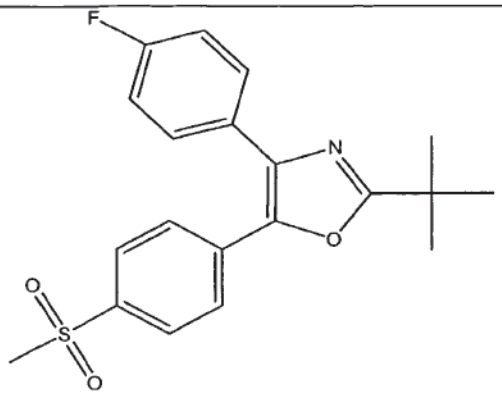
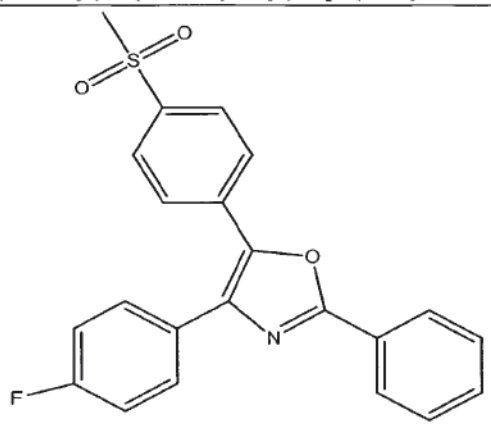
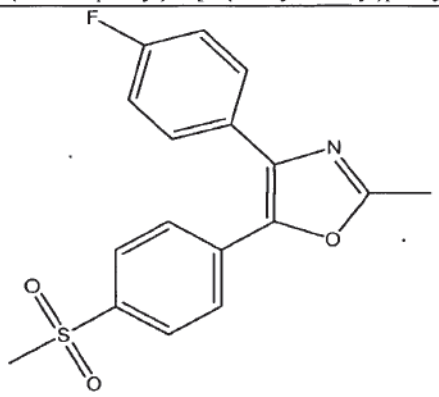
| Compound Number | Structural Formula |
|---|---|
| B-177 |  1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-178 |  1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-179 |  4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide; |

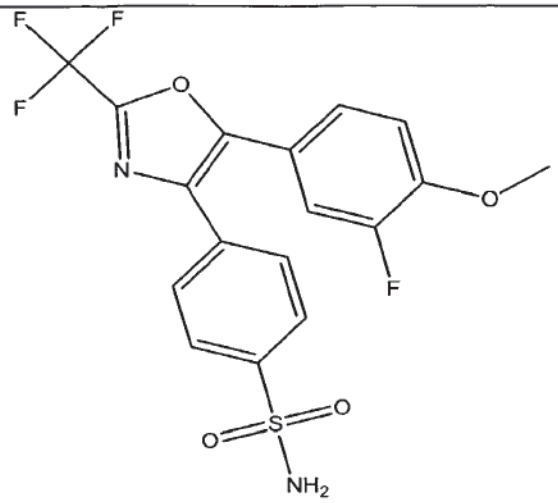
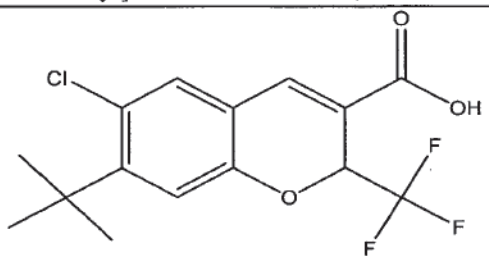
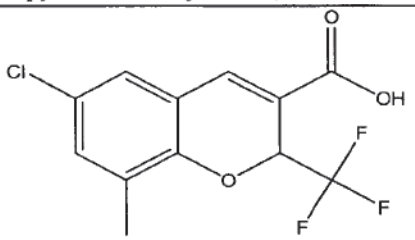
| Compound Number | Structural Formula |
|---|---|
| B-180 |  1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-181 |  4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide; |
| B-182 |  4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide; |

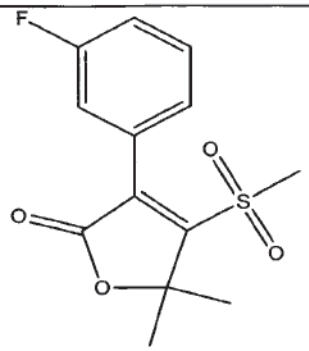
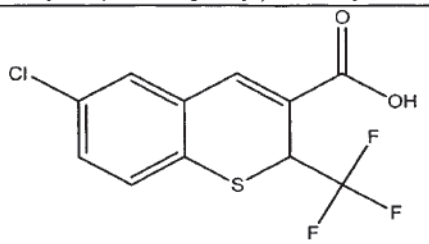
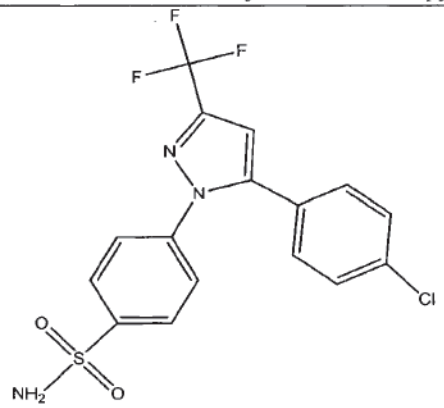
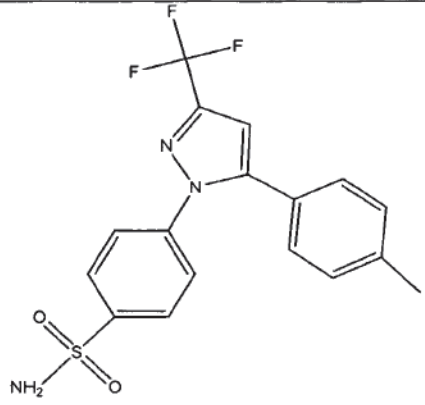
| Compound Number | Structural Formula |
|---|---|
| B-183 |  4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide; |
| B-184 |  1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-185 |  1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |

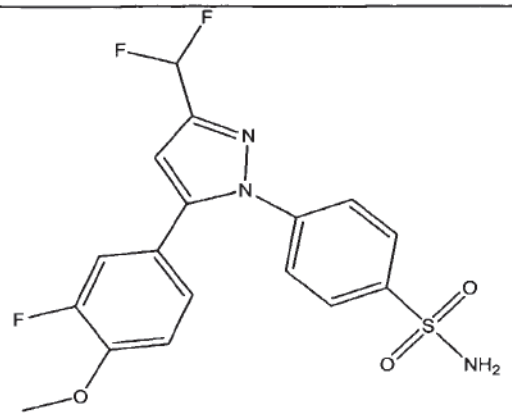
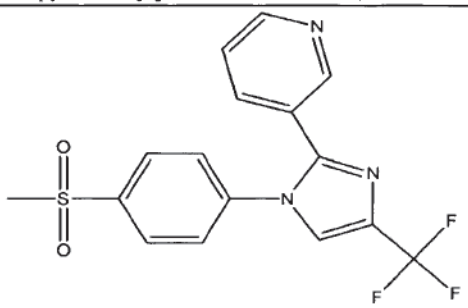
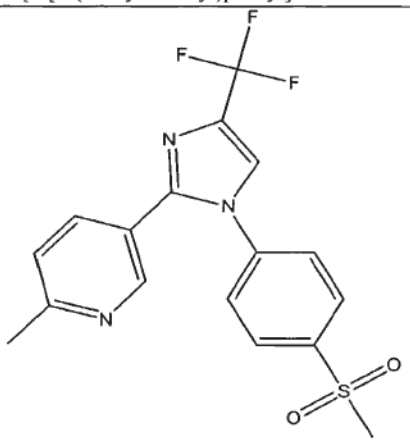
| Compound Number | Structural Formula |
|---|---|
| B-186 |  4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide; |
| B-187 |  1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; |
| B-188 |  4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide; |

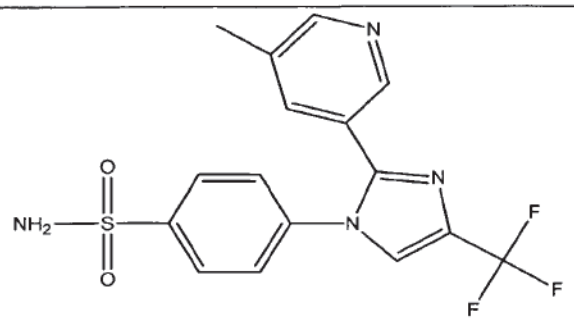
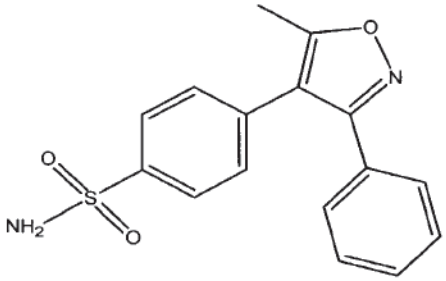
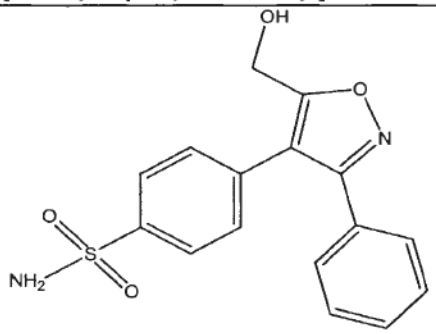
| Compound Number | Structural Formula |
|---|---|
| B-189 |  4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide; |
| B-190 |  ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate; |
| B-191 |  2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid; |

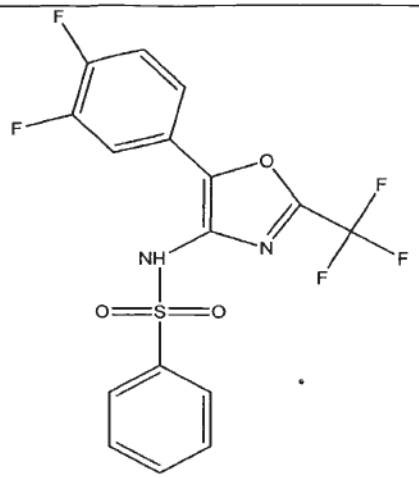
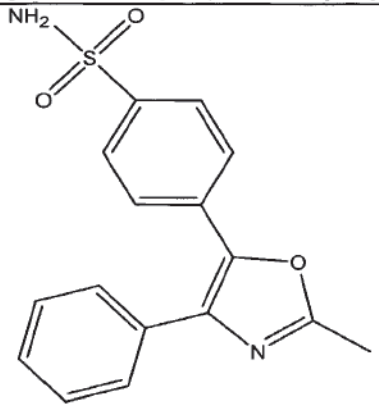
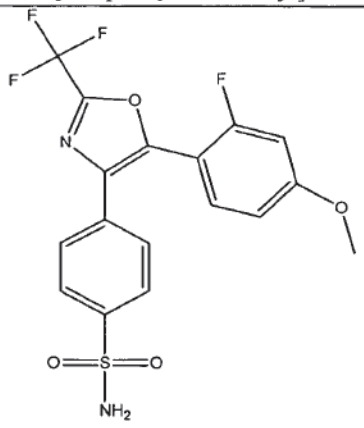
| Compound Number | Structural Formula |
|---|---|
| B-192 |  2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole; |
| B-193 |  4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole; |
| B-194 |  4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; |

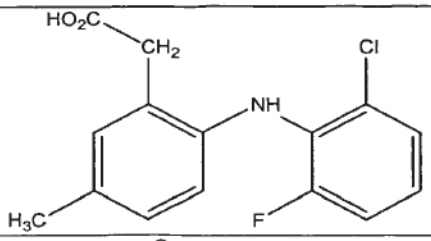
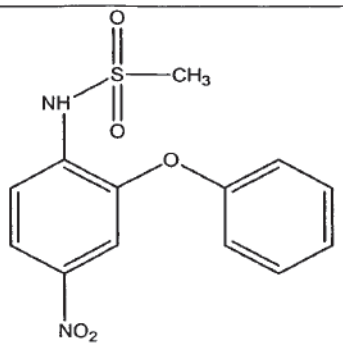
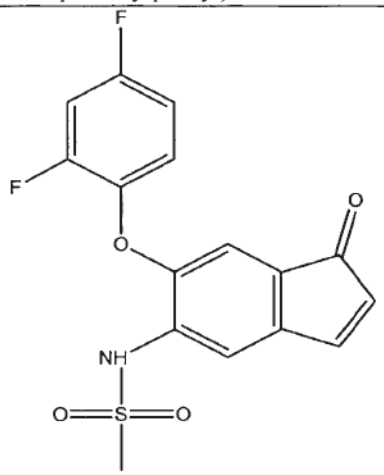
| Compound Number | Structural Formula |
|---|---|
| B-195 |  4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl -4-oxazolyl]benzenesulfonamide; |
| B-196 |  6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H -1-benzopyran-3-carboxylic acid; |
| B-197 |  6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; |

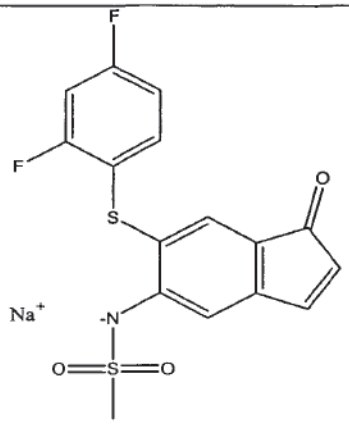
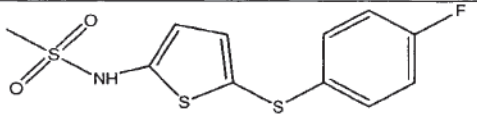
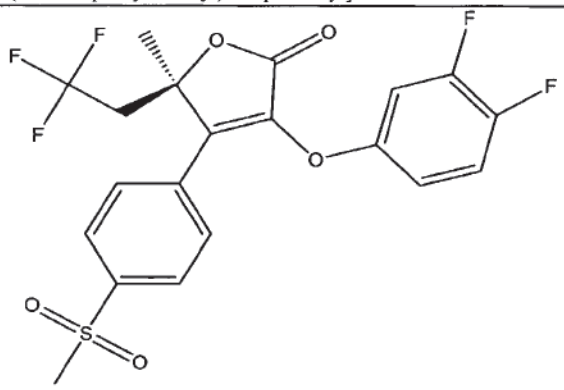
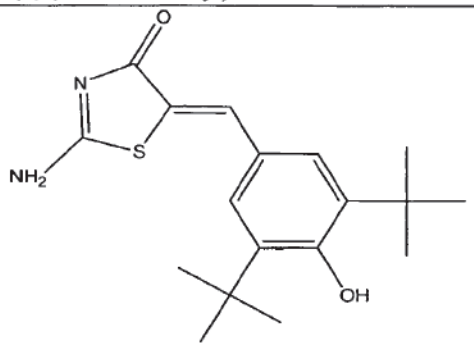
| Compound Number | Structural Formula |
|---|---|
| B-198 |  5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone; |
| B-199 |  6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid; |
| B-200 |  4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |
| B-201 |  4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; |

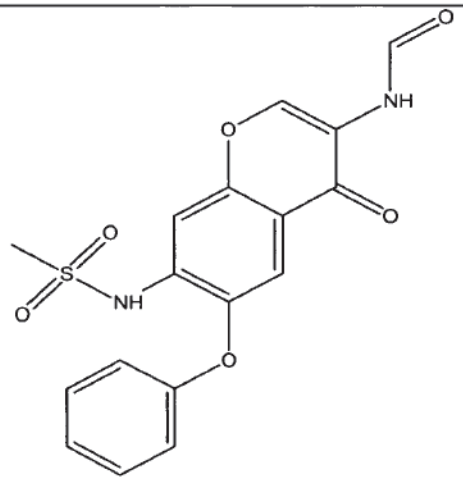
| Compound Number | Structural Formula |
|---|---|
| B-202 |  4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide; |
| B-203 |  3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; |
| B-204 |  2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl -1H-imidazol-2-yl]pyridine; |

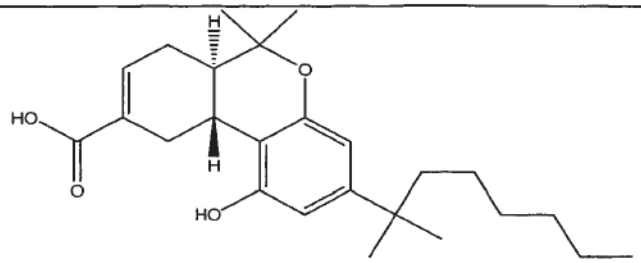
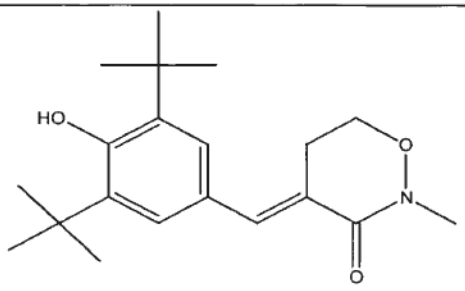
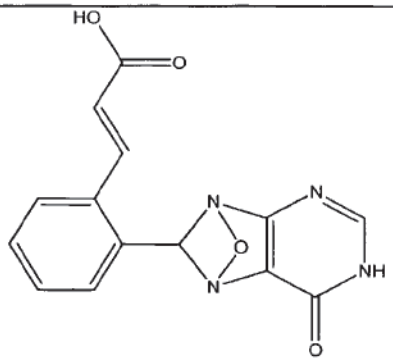
| Compound Number | Structural Formula |
|---|---|
| B-205 |  4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide; |
| B-206 |  4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide; |
| B-207 |  4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide; |

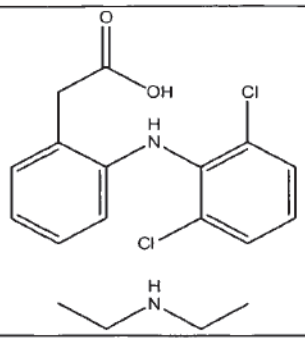
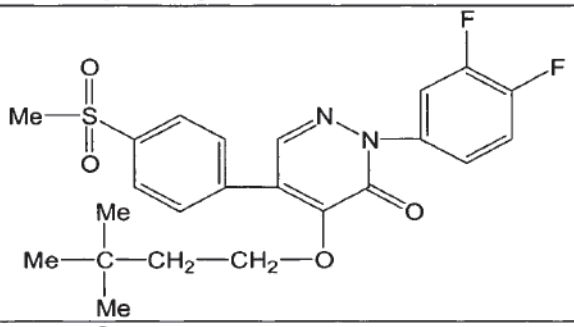
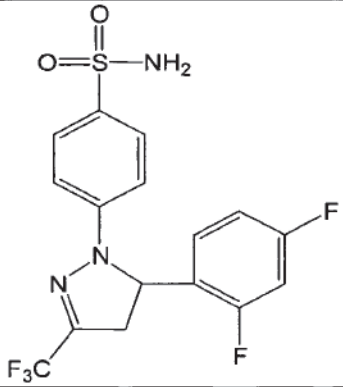
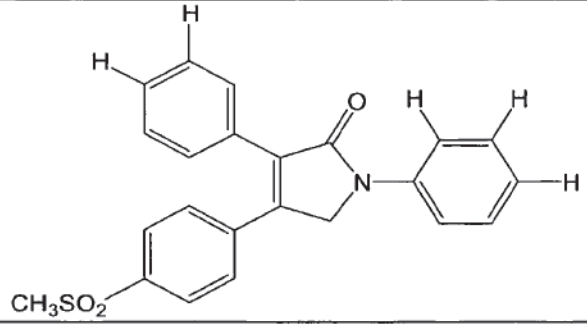
| Compound Number | Structural Formula |
|---|---|
| B-208 |  [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide; |
| B-209 |  4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; |
| B-210 |  4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide; |

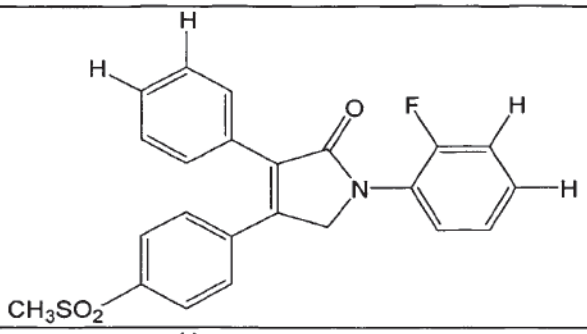
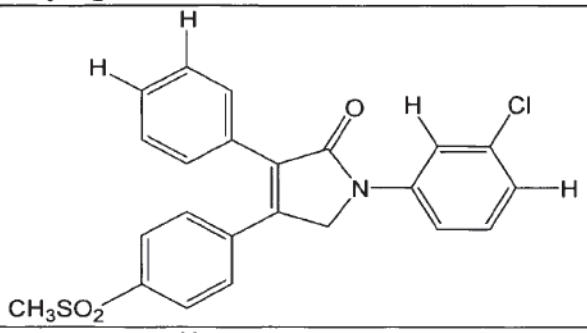
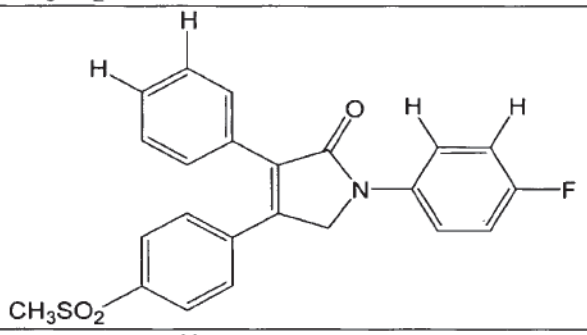
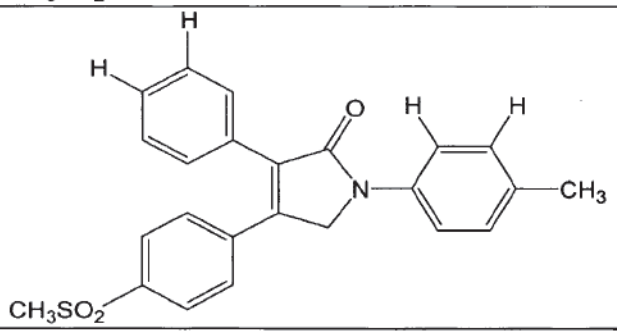
| Compound Number | Structural Formula |
|---|---|
| B-211 |  |
| B-212 |  *N*-(4-nitro-2-phenoxy-phenyl)-methanesulfonamide |
| B-213 |  N-[6-(2,4-difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide |

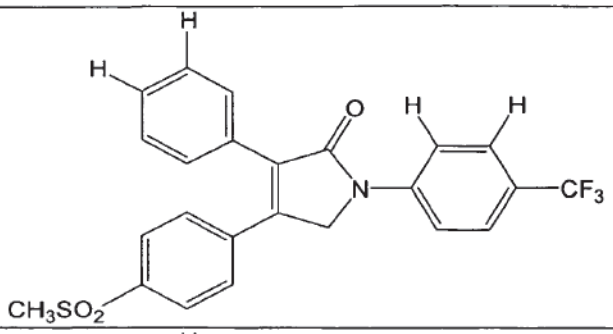
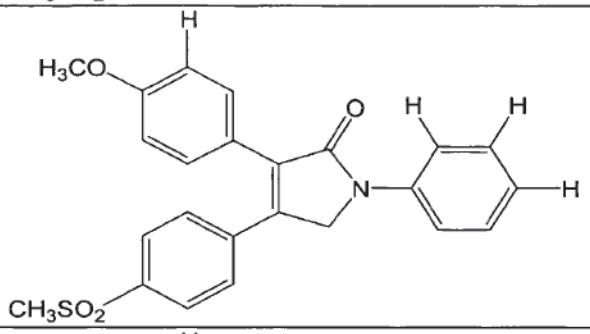
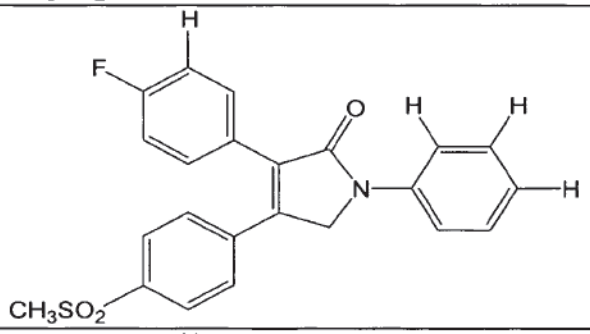
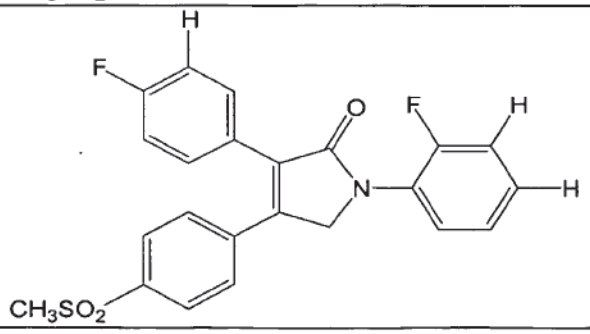
| Compound Number | Structural Formula |
|---|---|
| B-214 |  *N*-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt |
| B-215 |  N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide |
| B-216 |  3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one |
| B-217 |  (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] -4(5H)-thiazolone |

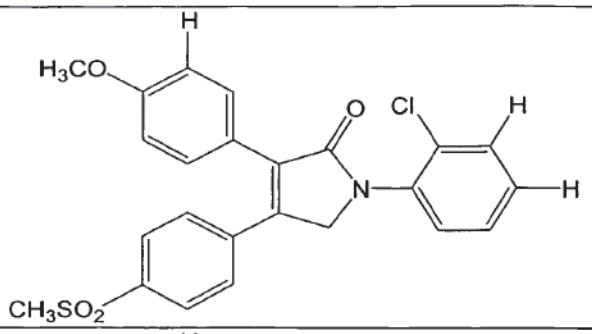
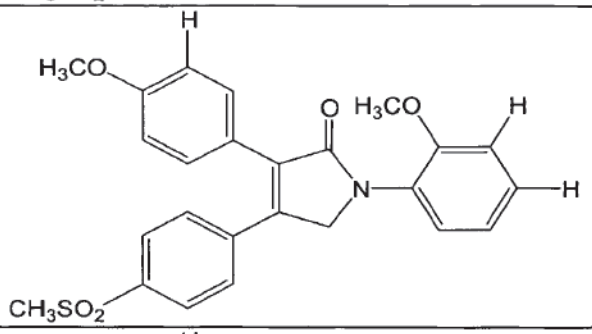
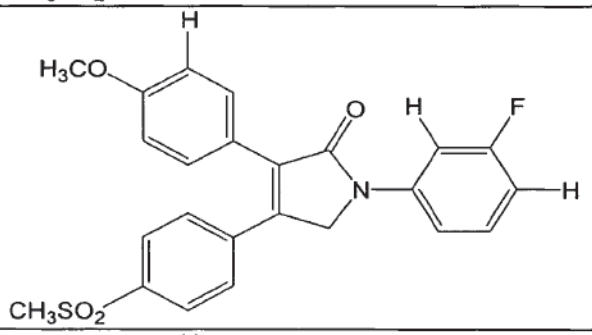
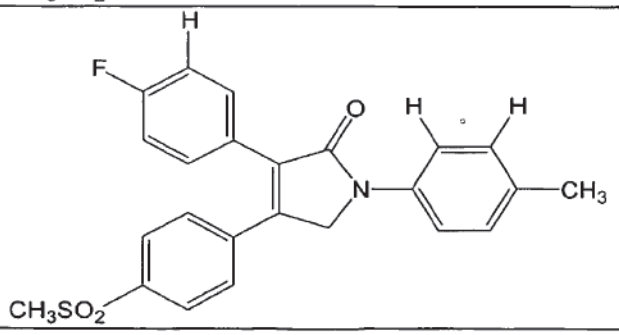
| Compound Number | Structural Formula |
|---|---|
| B-218 | CS-502 |
| B-219 | LAS-34475 |
| B-220 | LAS-34555 |
| B-221 | S-33516 |
| B-222 | SD-8381 |
| B-223 | L-783003 |
| B-224 |  N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] -methanesulfonamide |
| B-225 | D-1367 |
| B-226 | L-748731 |

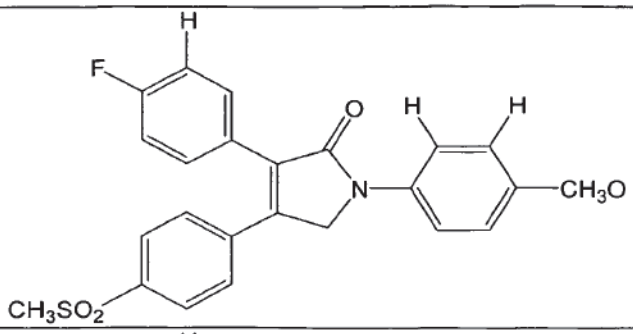
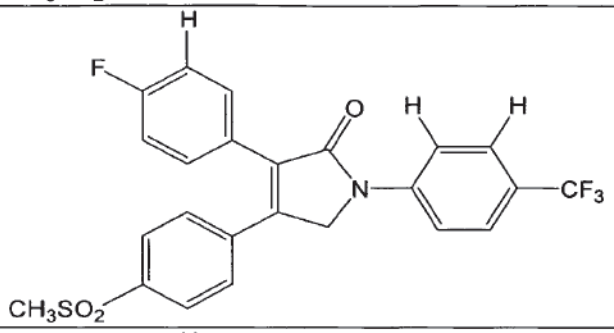
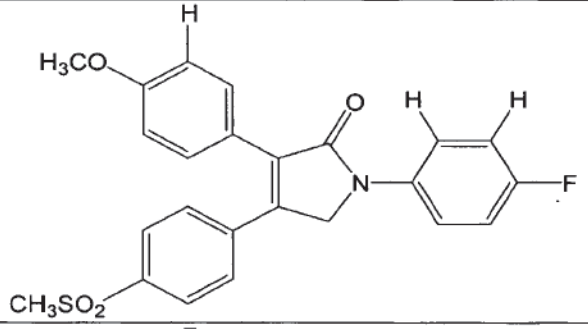
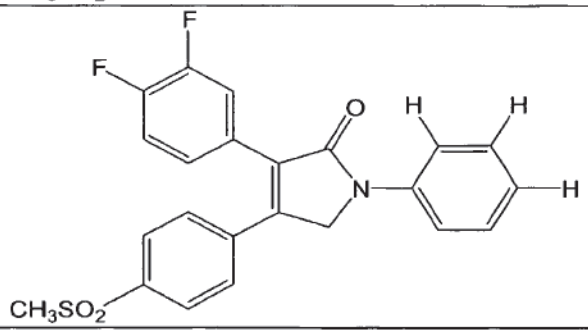
| Compound Number | Structural Formula |
|---|---|
| B-227 |  (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid |
| B-228 | CGP-28238 |
| B-229 |  4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one |
| B-230 | GR-253035 |
| B-231 |  2-(6-dioxo-9H-purin-8-yl)cinnamic acid |
| B-232 | S-2474 |

| Compound Number | Structural Formula |
|---|---|
| B-233 |  |
| B-234 |  |
| B-235 |  |
| B-236 |  |

| Compound Number | Structural Formula |
|---|---|
| B-237 |  |
| B-238 |  |
| B-239 |  |
| B-240 |  |

| Compound Number | Structural Formula |
|---|---|
| B-241 |  |
| B-242 |  |
| B-243 |  |
| B-244 |  |

| Compound Number | Structural Formula |
|---|---|
| B-245 |  |
| B-246 |  |
| B-247 |  |
| B-248 |  |

| Compound Number | Structural Formula |
|---|---|
| B-249 |  |
| B-250 |  |
| B-251 |  |
| B-252 |  |

[0415] The cyclooxygenase-2 selective inhibitor employed in the present invention can exist in tautomeric, geometric or stereoisomeric forms. Generally speaking, suitable cyclooxygenase-2 selective inhibitors that are in tautomeric, geometric or stereoisomeric forms are those compounds that inhibit cyclooxygenase-2 activity by about 25%, more typically by about 50%, and even more typically, by about

75% or more when present at a concentration of 100 μM or less. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures or R and S forms for each stereocenter present.

[0416] The cyclooxygenase-2 selective inhibitors utilized in the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for

example, the appropriate acid or base with the compound of any Formula set forth herein.

[0417] The cyclooxygenase-2 selective inhibitors of the present invention can be formulated into pharmaceutical compositions and administered by a number of different means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

[0418] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0419] Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0420] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are

ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0421] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0422] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0423] The amount of active ingredient that can be combined with the carrier materials to produce a single dosage of the cyclooxygenase-2 selective inhibitor will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, more typically, in the range of about 0.5 to 500 mg and still more typically, between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, or more typically, between about 0.1 and about 50 mg/kg body weight and even more typically, from about 1 to 20 mg/kg body weight, may be

appropriate. The daily dose is generally administered in one to about four doses per day.

[0424] In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is typical that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more typically, from about 0.18 to about 0.4 mg/day·kg.

[0425] In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is typical that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0426] Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is typical that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more typically, from about 1.4 to about 8.6 mg/day·kg, and yet more typically, from about 2 to about 3 mg/day·kg.

[0427] When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0428] In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 1 to about 3 mg/day·kg.

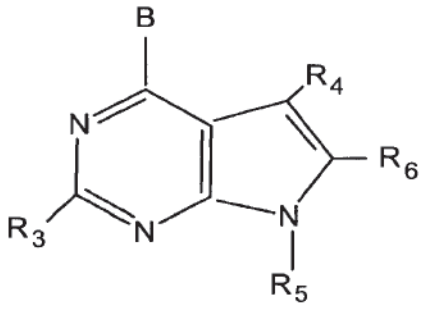
[0429] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

[0430] In addition to a cyclooxygenase-2 selective inhibitor, the combination therapy of the present invention comprises a corticotropin releasing factor antagonist. In one embodiment, the corticotropin releasing factor antagonist in this therapeutic combination is selected from the group consisting of $\alpha$-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695 (N-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-

methoxyethyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine mesylate)), D-PheCRF 12-41, and N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine. In one embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41, antalarmin, CP-154,526, and astressin. In another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41 and antalarmin. In yet another embodiment, the corticotropin releasing factor antagonist of this therapeutic combination is *α*-helical CRF 9-41.

[0431] In one embodiment, the corticotropin releasing factor antagonist is represented by Formula *(VI)*:




**(VI)**

[0432] wherein:

[0433] B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCR_1R_2R_{11}$, $-OCR_1R_2R_{11}$, $-SCR_1R2R_{11}$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$, $-CR_2R_{11}OR_1$, $-CR_2R_{11}SR_1$, or $-C(O)R_2$;

[0434] $R_1$ is hydrogen, or $C_1$-$C_6$ alkyl optionally substituted with from one to two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, $C_1$-$C_8$ alkoxy, -O($C_1$-$C_6$ alkyl), -ONH($C_1$-$C_4$ alkyl), -ON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), amino, -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_4$ alkyl), -NH($C_1$-$C_4$ alkyl), -COOH, -O($C_1$-$C_4$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -SH, -CN, $-NO_2$, -SO($C_1$-$C_4$ alkyl), $-SO_2$ ($C_1$-$C_4$ alkyl), $-SO_2$ NH($C_1$-$C_4$ alkyl), $-SO_2$ ($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and wherein each of the foregoing $C_1$-$C_6$ alkyl moieties in the definition of $R_1$ may contain one or two double or triple bonds;

[0435] $R_2$ is $C_1$-$C_{12}$ alkyl, aryl or ($C_1$-$C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl,

furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1$-$C_6$ alkylene) cycloalkyl, wherein one or two of the carbon atoms of any of said cycloalkyl moieties may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkanoyl, and wherein $R_2$ may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and $C_1$-$C_4$ alkyl, or by one substituent selected from hydroxy, bromo, iodo, $C_1$-$C_6$ alkoxy, -O($C_1$-$C_6$ alkyl), -ON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_6$ alkyl), -$NH_2$, -NH($C_1$-$C_2$ alkyl), -N($C_1$-$C_2$ alkyl) ($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)-($C_1$-$C_4$ alkyl), -NH($C_1$-$C_4$ alkyl), -COOH, -O($C_1$-$C_4$ alkyl), -NH(C1-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -SH, -CN, -$NO_2$, -SO($C_1$-$C_4$ alkyl), -$SO_2$ ($C_1$-$C_4$ alkyl), -$SO_2$NH($C_1$-$C_4$ alkyl), and -$SO_2$N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and wherein each of the foregoing $C_1$-$C_{12}$ alkyl and $C_1$-$C_{10}$ alkylene moieties in the definition may optionally contain one to three double or triple bonds; or $R_1$ and $R_2$, taken together with the atom to which they are attached, may form a saturated 3- to 8-membered ring which, if it is a 5- to 8-membered ring, may optionally contain one to two double bonds, and wherein one or two of the carbon atoms of said 5- to 8- membered ring may optionally be replaced, independently, by O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl or benzyl;

[0436] $R_3$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, -O($C_1$-$C_6$ alkyl), -NH($C_1$-$C_6$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -SH, -S($C_1$-$C_4$ alkyl), -SO($C_1$-$C_4$ alkyl), or -$SO_2$ ($C_1$-$C_4$ alkyl), wherein each of the foregoing $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl moieties in the definition of $R_3$ may contain one double or triple bond and may optionally be substituted with from 1 to 3 substituents independently selected from the group consisting of hydroxy, $C_1$-$C_3$ alkoxy, fluoro, chloro or $C_1$-$C_3$ thioalkyl;

[0437] $R_4$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, -NH($C_1$-$C_6$ alkyl), -N($C_1$-$C_6$ alkyl)($C_1$-$C_2$ alkyl), -$SO_n$ ($C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein each of the foregoing $C_1$-$C_6$ alkyl moieties in the definition of $R_4$ may optionally be substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -O($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0438] $R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl,

benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolindinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or a 3- or 8-membered cycloalkyl or 9- or 12-membered bicycloalkyl ring, wherein one or two of the carbon atoms in said ring may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or benzyl, and wherein each of the above $R_5$ groups may optionally be substituted with one or more substituents, preferably with two or three substituents, independently selected from fluoro, chloro, bromo, formyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy and trifluoromethyl, or with one substituent selected from hydroxy, iodo, cyano, nitro, amino, -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -COO($C_1$-$C_4$ alkyl), -CO($C_1$-$C_4$ alkyl), -$SO_2$NH($C_1$-$C_4$ alkyl), -$SO_2$N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -$SO_2NH_2$, -NH$SO_2$($C_1$-$C_4$ alkyl), -S($C_1$-$C_6$ alkyl), -$SO_2$($C_1$-$C_6$ alkyl), and wherein each of the foregoing $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl moieties in the definition of $R_5$ may optionally be substituted with from one to two substituents independently selected from fluoro, chloro, hydroxy, $C_1$-$C_4$ alkoxy, amino, methylamino, dimethylamino and acetyl, and wherein each of the foregoing $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl moieties in the definition of $R_5$ may optionally contain one double or triple bond; with the proviso that $R_5$ is not unsubstituted phenyl;

[0439] $R_6$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, amino, -NH($C_1$-$C_6$ alkyl), -N($C_1$-$C_6$ alkyl)($C_1$-$C_2$ alkyl), -$SO_n$($C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, and wherein each of the foregoing ($C_1$-$C_6$)alkyl moieties in the definition of $R_6$ may be optionally substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -O($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0440] $R_7$ is hydrogen, hydroxy, fluoro, chloro, -COO($C_1$-$C_2$ alkyl), cyano, or -CO($C_1$-$C_2$ alkyl); and

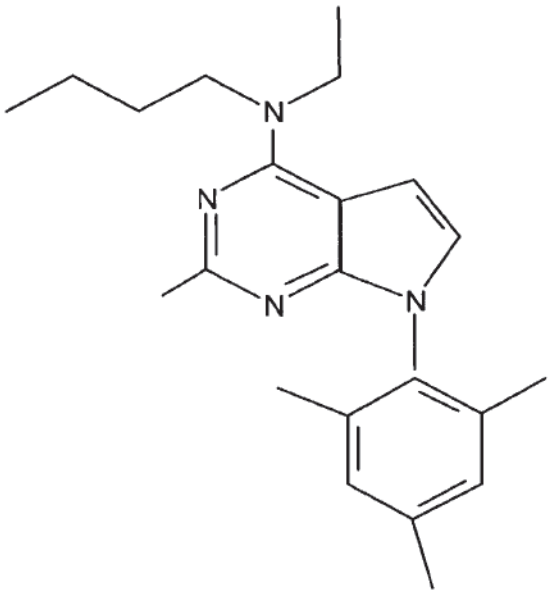
[0441] $R_8$ is hydrogen or $C_1$-$C_4$ alkyl;

[0442] with the proviso that:

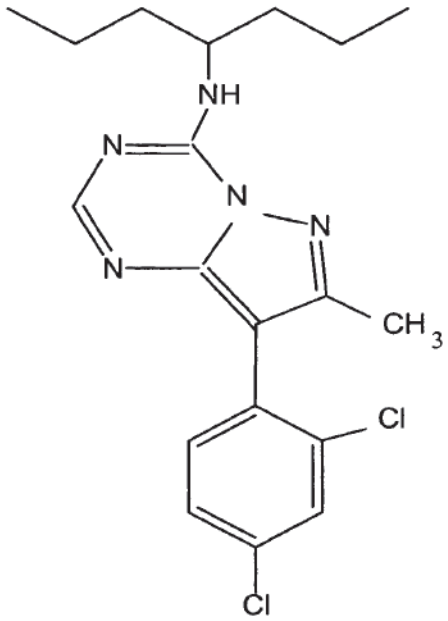
[0443] B is not a straight chain alkyl when $R_5$ is unsubstituted cycloalkyl, $R_3$ and $R_4$ are both hydrogen and $R_6$ is hydrogen or methyl; B is not $NHR_2$ wherein $R_2$ is benzyl or thienylmethyl; and B is not methylamino or hydroxyethylamino when $R_5$ is p-bromophenyl and $R_3$, $R_4$ and $R_6$ are methyl.

[0444] Suitable examples of compounds having formula VI are described in WO 94/13676, which is hereby incorporated by reference in its entirety.

[0445] In another embodiment, the corticotropin releasing factor antagonist is CP-154,526, having the formula:



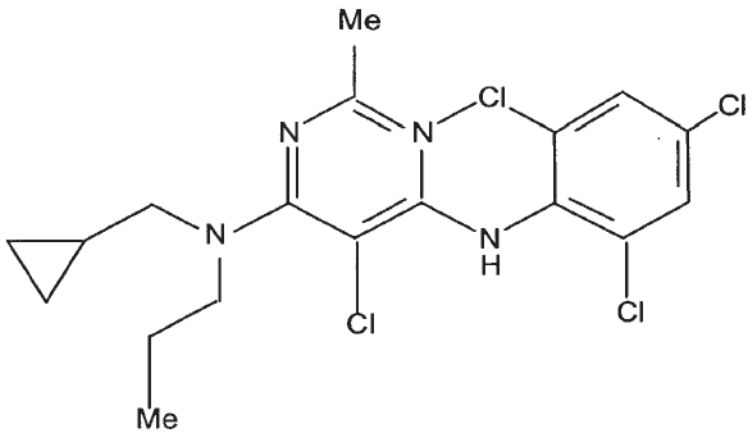
[0446] In yet another embodiment of the invention, the corticotropin releasing factor antagonist is DMP 696, having the formula:



[0447] In still another embodiment of the invention, the corticotropin releasing factor antagonist is $\alpha$-helical CRF 9-41, having the sequence:

[0448] Asp-Leu-Thr-Phe-His-Leu-Arg-Glu-Met-Leu-Glu-Met-Ala-Lys-ala-Glu-Gln-Ala-Glu-Gln-Ala-Leu-Asn-Arg-Leu-Leu-Glu-Ala-NH2 (Sequence ID No.1).

[0449] In another embodiment of the invention, the corticotropin releasing factor antagonist is NBI 27914 hydrochloride, having the formula:




[0450] Generally speaking, the corticotropin releasing antagonist can be administered as a pharmaceutical composition with or without a carrier. The terms "pharmaceutically acceptable carrier" or "carrier" refer to any generally acceptable excipient or drug delivery composition that is relatively inert and non-toxic. Exemplary carriers include sterile water, salt solutions (such as Ringer's solution), alcohols, gelatin, talc, viscous paraffin, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, calcium carbonate, carbohydrates (such as lactose, sucrose, dextrose, mannose, albumin, starch), cellulose, silica gel, polyethylene glycol (PEG), dried skim milk, rice flour, magnesium stearate, and the like. Suitable formulations and additional carriers are described in Remington's Pharmaceutical Sciences, (17.sup.th Ed., Mack Pub. Co., Easton, Pa.). Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include, potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc. The compositions can also be combined

where desired with other active substances, e.g., enzyme inhibitors, to reduce metabolic degradation.

[0451] Moreover, the corticotropin releasing antagonist can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The method of administration can dictate how the composition will be formulated. For example, the composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, or magnesium carbonate.

[0452] In another embodiment, the corticotropin releasing antagonist can be administered intravenously, parenterally, intramuscularly, subcutaneously, orally, nasally, topically, by inhalation, by implant, by injection, or by suppository. For enteral or mucosal application (including via oral and nasal mucosa), particularly suitable are tablets, liquids, drops, suppositories or capsules. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Liposomes, microspheres, and microcapsules are available and can be used. Pulmonary administration can be accomplished, for example, using any of various delivery devices known in the art such as an inhaler. See. e.g. S. P. Newman (1984) in Aerosols and the Lung, Clarke and Davis (eds.), Butterworths, London, England, pp. 197-224; PCT Publication No. WO 92/16192; PCT Publication No. WO 91/08760. For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like.

[0453] The actual effective amounts of compound or drug can and will vary according to the specific composition being utilized, the mode of administration and the age, weight and condition of the subject. Dosages for a particular individual subject can be determined by one of ordinary skill in the art using conventional considerations.

[0454] By way of example, in one embodiment when the corticotropin releasing antagonist is $\alpha$-helical CRF 9-41, the amount administered daily is typically from about 0.5 to about 3500 milligrams. In an alternative of this embodiment, the amount of $\alpha$-helical CRF 9-41 administered daily is between about 1 and about 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment,

the amount of α-helical CRF 9-41 administered daily is between about 5 and about 20 milligrams/kilogram of the subject's weight.

[0455] By way of further example, in another embodiment the corticotropin releasing antagonist is antalarmin, and the amount administered daily is typically from about 50 to about 4000 miligrams. In an alternative of this embodiment, the amount of antalarmin administered daily is between about 1 and 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment, the amount of antalarmin administered daily is between about 5 and about 30 milligrams/kilogram of the subject's weight.

[0456] Moreover, the corticotropin releasing factor antagonist can be a combination of two or more different corticotropin releasing antagonists. The multiple antagonists can be administered separately or may be co-administered as a single composition and may be administered as discussed above.

[0457] By way of example, in another embodiment the corticotropin releasing antagonist is a combination of α-helical CRF 9-41 and antalarmin, and the amount of the combination antagonist administered daily is typically from about 0.1 to about 1000 μg. In an alternative of this embodiment, the amount of the combination antagonist administered daily is between about 1 and 50 milligrams/ kilogram of the subject's weight. In another alternative of this embodiment, the amount of the combination antagonist administered daily is between about 5 and about 25 milligrams/ kilogram of the subject's weight.

[0458] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0459] Generally speaking, when the composition is administered to treat an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject as soon as possible after the reduction in blood flow to the central nervous system in order to reduce the extent of ischemic damage. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 10 days after the reduction of blood flow to the central nervous system and more typically, within 24 hours. In still another embodiment, the corticotropin releasing factor antagonist and

cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours after the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours after the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours after the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours after the reduction in blood flow to the central nervous system.

[0460] Generally speaking, when the composition is administered to prevent an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject such that the antagonist has sufficient time to bind to the corticotropin releasing factor receptors and/or to exact its preventative effects. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 24 hours before the reduction of blood flow to the central nervous system and more typically, within about 12 hours. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours before the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours before the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours before the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours before the reduction in blood flow to the central nervous system. In still a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1 hour before the reduction in blood flow to the central nervous system. In still yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1/2 hour before the reduction in blood flow to the central nervous system.

[0461] Moreover, the timing of the administration of the cyclooxygenase-2 selective inhibitor in relation to the administration of the corticotropin releasing factor antagonist may also vary from subject to subject. In one embodiment, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered substantially simultaneously, meaning that each agent may be administered to the subject at approximately the same time. For example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning on the same day as the beginning of the corticotropin releasing factor antagonist and extending to a period after the end of the corticotropin releasing factor antagonist. Alternatively, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered sequentially, meaning that they are each administered at separate times during separate treatments. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning prior to administration of the corticotropin releasing factor antagonist and ending after administration of the corticotropin releasing factor antagonist. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the corticotropin releasing factor antagonist. Moreover, it will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention.

COMBINATION THERAPIES

[0462] Generally speaking, it is contemplated that the composition employed in the practice of the invention may include one or more of any of the cyclooxygenase-2 selective inhibitors detailed above in combination with one or more of any of the corticotropin releasing factor antagonists detailed above. By way of a non-limiting example, Table 4a details a number of suitable combinations that are useful in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4a.

TABLE 4a

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing Factor Antagonist |
|---|---|
| a compound having formula I | α-helical CRF 9-41 |
| a compound having formula I | antalarmin |
| a compound having formula I | astressin |
| a compound having formula I | NBI 27914 |
| a compound having formula I | R121919 |
| a compound having formula I | R121920 |
| a compound having formula I | antisauvagine-30 |
| a compound having formula I | DMP-695 |
| a compound having formula I | CP-154,526 |
| a compound having formula II | α-helical CRF 9-41 |
| a compound having formula II | antalarmin |
| a compound having formula II | astressin |
| a compound having formula II | NBI 27914 |
| a compound having formula II | R121919 |
| a compound having formula II | R121920 |
| a compound having formula II | antisauvagine-30 |
| a compound having formula II | DMP-695 |
| a compound having formula II | CP-154,526 |
| a compound having formula III | α-helical CRF 9-41 |
| a compound having formula III | antalarmin |
| a compound having formula III | astressin |
| a compound having formula III | NBI 27914 |
| a compound having formula III | R121919 |
| a compound having formula III | R121920 |
| a compound having formula III | antisauvagine-30 |
| a compound having formula III | DMP-695 |
| a compound having formula III | CP-154,526 |
| a compound having formula IV | α-helical CRF 9-41 |
| a compound having formula IV | antalarmin |
| a compound having formula IV | astressin |
| a compound having formula IV | NBI 27914 |
| a compound having formula IV | R121919 |
| a compound having formula IV | R121920 |
| a compound having formula IV | antisauvagine-30 |
| a compound having formula IV | DMP-695 |
| a compound having formula IV | CP-154,526 |
| a compound having formula V | α-helical CRF 9-41 |
| a compound having formula V | antalarmin |
| a compound having formula V | astressin |
| a compound having formula V | NBI 27914 |
| a compound having formula V | R121919 |
| a compound having formula V | R121920 |
| a compound having formula V | antisauvagine-30 |
| a compound having formula V | DMP-695 |
| a compound having formula V | CP-154,526 |

[0463] By way of further example, Table 4b details a number of suitable combinations that may be employed in the methods and compositions of the present invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4b.

TABLE 4b

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | $\alpha$-helical CRF 9-41 |

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | antalarmin |

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | astressin |

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | NBI 27914 |

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | R121919 |

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | R121920 |

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| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | antisauvagine-30 |

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|---|---|
| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | DMP-695 |

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|---|---|
| a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252. | CP-154,526 |

[0464] By way of yet further example, Table 4c details additional suitable combinations that may be employed in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4c.

TABLE 4c

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing factor Antagonist |
|---|---|
| Celecoxib | α-helical CRF 9-41 |
| Celecoxib | antalarmin |
| Celecoxib | astressin |
| Celecoxib | NBI 27914 |
| Celecoxib | R121919 |
| Celecoxib | R121920 |
| Celecoxib | antisauvagine-30 |
| Celecoxib | DMP-695 |
| Celecoxib | CP-154,526 |
| Cimicoxib | α-helical CRF 9-41 |
| Cimicoxib | antalarmin |
| Cimicoxib | astressin |
| Cimicoxib | NBI 27914 |
| Cimicoxib | R121919 |
| Cimicoxib | R121920 |
| Cimicoxib | antisauvagine-30 |
| Cimicoxib | DMP-695 |
| Cimicoxib | CP-154,526 |
| Deracoxib | α-helical CRF 9-41 |
| Deracoxib | antalarmin |
| Deracoxib | astressin |
| Deracoxib | NBI 27914 |
| Deracoxib | R121919 |
| Deracoxib | R121920 |
| Deracoxib | antisauvagine-30 |
| Deracoxib | DMP-695 |
| Deracoxib | CP-154,526 |
| Valdecoxib | α-helical CRF 9-41 |
| Valdecoxib | antalarmin |
| Valdecoxib | astressin |
| Valdecoxib | NBI 27914 |
| Valdecoxib | R121919 |
| Valdecoxib | R121920 |
| Valdecoxib | antisauvagine-30 |
| Valdecoxib | DMP-695 |
| Valdecoxib | CP-154,526 |
| Rofecoxib | α-helical CRF 9-41 |
| Rofecoxib | antalarmin |
| Rofecoxib | astressin |
| Rofecoxib | NBI 27914 |
| Rofecoxib | R121919 |
| Rofecoxib | R121920 |
| Rofecoxib | antisauvagine-30 |
| Rofecoxib | DMP-695 |
| Rofecoxib | CP-154,526 |
| Etoricoxib | α-helical CRF 9-41 |

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing factor Antagonist |
|---|---|
| Etoricoxib | antalarmin |
| Etoricoxib | astressin |
| Etoricoxib | NBI 27914 |
| Etoricoxib | R121919 |
| Etoricoxib | R121920 |
| Etoricoxib | antisauvagine-30 |
| Etoricoxib | DMP-695 |
| Etoricoxib | CP-154,526 |
| Meloxicam | $\alpha$-helical CRF 9-41 |
| Meloxicam | antalarmin |
| Meloxicam | astressin |
| Meloxicam | NBI 27914 |
| Meloxicam | R121919 |
| Meloxicam | R121920 |
| Meloxicam | antisauvagine-30 |
| Meloxicam | DMP-695 |
| Meloxicam | CP-154,526 |
| Parecoxib | $\alpha$-helical CRF 9-41 |
| Parecoxib | antalarmin |
| Parecoxib | astressin |
| Parecoxib | NBI 27914 |
| Parecoxib | R121919 |
| Parecoxib | R121920 |
| Parecoxib | antisauvagine-30 |
| Parecoxib | DMP-695 |
| Parecoxib | CP-154,526 |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | $\alpha$-helical CRF 9-41 |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | antalarmin |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | astressin |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | NBI 27914 |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | R121919 |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | R121920 |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | antisauvagine-30 |

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing factor Antagonist |
|---|---|
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | DMP-695 |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | CP-154,526 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | α-helical CRF 9-41 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | antalarmin |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | astressin |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | NBI 27914 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | R121919 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | R121920 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | antisauvagine-30 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | DMP-695 |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | CP-154,526 |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | α-helical CRF 9-41 |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | antalarmin |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | astressin |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | NBI 27914 |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | R121919 |

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing factor Antagonist |
|---|---|
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | R121920 |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | antisauvagine-30 |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | DMP-695 |
| N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide | CP-154,526 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | $\alpha$-helical CRF 9-41 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | antalarmin |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | astressin |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | NBI 27914 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | R121919 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | R121920 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | antisauvagine-30 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | DMP-695 |
| 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone | CP-154,526 |

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing factor Antagonist |
|---|---|
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | $\alpha$-helical CRF 9-41 |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | antalarmin |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | astressin |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | NBI 27914 |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | R121919 |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | R121920 |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | antisauvagine-30 |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | DMP-695 |
| 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid | CP-154,526 |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | $\alpha$-helical CRF 9-41 |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | antalarmin |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | astressin |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | NBI 27914 |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | R121919 |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | R121920 |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | antisauvagine-30 |

| Cyclooxygenase-2 Selective Inhibitor | Corticotropin Releasing factor Antagonist |
|---|---|
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | DMP-695 |
| (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone | CP-154,526 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | *α*-helical CRF 9-41 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | antalarmin |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | astressin |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | NBI 27914 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | R121919 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | R121920 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | antisauvagine-30 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | DMP-695 |
| (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid | CP-154,526 |
| Lumiracoxib | *α*-helical CRF 9-41 |
| Lumiracoxib | antalarmin |
| Lumiracoxib | astressin |
| Lumiracoxib | NBI 27914 |
| Lumiracoxib | R121919 |
| Lumiracoxib | R121920 |
| Lumiracoxib | antisauvagine-30 |
| Lumiracoxib | DMP-695 |
| Lumiracoxib | CP-154,526 |

DIAGNOSIS OF A VASO-OCCLUSION

[0100] One aspect of the invention encompasses diagnosing a subject in need of treatment or prevention for a vaso-occlusive event. A number of suitable methods for diagnosing a vaso-occlusion may be used in the practice of the invention.

In one such method, ultrasound may be employed. This method examines the blood flow in the major arteries and veins in the arms and legs with the use of ultrasound (high-frequency sound waves). In one embodiment, the test may combine Doppler® ultrasonography, which uses audio measurements to "hear" and measure the blood flow and duplex ultrasonography, which provides a visual image. In an alternative embodiment, the test may utilize multifrequency ultrasound or multifrequency transcranial Doppler® (MTCD) ultrasound.

Another method that may be employed encompasses injection of the subject with a compound that can be imaged. In one alternative of this embodiment, a small amount of radioactive material is injected into the subject and then standard techniques that rely on monitoring blood flow to detect a blockage, such as magnetic resonance direct thrombus imaging (MRDTI), may be utilized to image the vaso-occlusion. In an alternative embodiment, ThromboView® (commercially available from Agenix Limited) uses a clot-binding monoclonal antibody attached to a radiolabel. In addition to the methods identified herein, a number of other suitable methods known in the art for diagnosis of vaso-occlusive events may be utilized.

INDICATIONS TO BE TREATED

[0465] Typically, the composition comprising a therapeutically effective amount of a cyclooxygenase-2 selective inhibitor and a therapeutically effective amount of a corticotropin releasing factor antagonist may be employed to treat a number of ischemic mediated central nervous system disorders or injuries.

[0466] In some aspects, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. By way of example, the normal amount of perfusion to brain gray matter in humans is about 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs when the flow of blood falls below approximately 8-10 mL/100 g of brain tissue/min, while at slightly higher levels (i.e. 20-35 mL/100 g of brain tissue/min) the tissue remains alive but not able to function. In one embodiment, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0467] Another aspect encompasses administrating the composition to a subject to treat a central nervous system ischemic condition. A number of central nervous system ischemic conditions may be treated by the composition of the invention. In one embodiment, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytoxic edema or central nervous system tissue anoxemia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. Generally speaking, brain stem strokes strike the brain stem, which control involuntary life-support functions such as breathing, blood pressure, and heartbeat. In another alternative of this embodiment, the stroke is a cerebellar stroke. Typically, cerebellar strokes impact the cerebellum area of the brain, which controls balance and coordination. In still another embodiment, the stroke is an embolic stroke. In general terms, embolic strokes may impact any region of the brain and typically result from the blockage of an artery by a vaso-occlusion. In yet another alternative, the stroke may be a hemorrhagic stroke. Like embolic strokes, hemorrhagic stroke may impact any region of the brain, and typically result from a ruptured blood vessel characterized by a hemorrhage (bleeding) within or surrounding the brain. In a further embodiment, the stroke is a thrombotic stroke. Typically, thrombotic strokes result from the blockage of a blood vessel by accumulated deposits.

[0468] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure. By way of example, the subject may be undergoing heart surgery, lung surgery, spinal surgery, brain surgery, vascular surgery, abdominal surgery, or organ transplantation surgery. The organ transplantation surgery may include heart, lung, pancreas or liver transplantation surgery. Moreover, the central nervous system ischemic condition may occur as a result of a trauma or injury to a part of the subject's body outside the central nervous system. By way of example, the trauma or injury may cause a degree of bleeding that significantly reduces the total volume of blood in the subject's body.

Because of this reduced total volume, the amount of blood flow to the central nervous system is concomitantly reduced. By way of further example, the trauma or injury may also result in the formation of a vaso-occlusion that restricts blood flow to the central nervous system.

[0469] Of course it is contemplated that the composition may be employed to treat the central nervous system ischemic condition irrespective of the cause of the condition. In one embodiment, the ischemic condition results from a vaso-occlusion. The vaso-occlusion may be any type of occlusion, but is typically a cerebral thrombosis or a cerebral embolism. In a further embodiment, the ischemic condition may result from a hemorrhage. The hemorrhage may be any type of hemorrhage, but is generally a cerebral hemorrhage or a subararachnoid hemorrhage. In still another embodiment, the ischemic condition may result from the narrowing of a vessel. Generally speaking, the vessel may narrow as a result of a vasoconstriction such as occurs during vasospasms, or due to arteriosclerosis. In yet another embodiment, the ischemic condition results from an injury to the brain or spinal cord.

[0470] In yet another aspect, the composition is administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, the composition may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition

[0471] In a further aspect, the invention provides treatment for subjects who are at risk of a vaso-occlusive event. These subjects may or may not have had a previous vaso-occlusive event. The invention embraces the treatment of subjects prior to a vaso-occlusive event, at a time of a vaso-occlusive event and following a vaso-occlusive event. Thus, as used herein, the "treatment" of a subject is intended to embrace both prophylactic and therapeutic treatment, and can be used either to limit or to eliminate altogether the symptoms or the occurrence of a vaso-occlusive event.

[0472] In addition to a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist, the composition of the invention may also include any agent that ameliorates the effect of a reduction in blood flow to the central nervous system. In one embodiment, the agent is an anticoagulant including thrombin inhibitors such as heparin and Factor Xa inhibitors such as warafin. In an additional embodiment, the agent is an anti-platelet inhibitor such as a GP IIb/IIIa inhibitor. In a further embodiment, the agent is selected from tissue plasminogen activator (t-PA), streptokinase, and

urokinase. Additional agents include but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin $B_6$ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin $B_{12}$ (also known as cyanocobalamin); ß-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

[0473] In a further aspect, the composition may be employed to reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury. Traumatic brain or spinal cord injury may result from a wide variety of causes including, for example, blows to the head or back from objects; penetrating injuries from missiles, bullets, and shrapnel; falls; skull fractures with resulting penetration by bone pieces; and sudden acceleration or deceleration injuries. The composition of the invention may be beneficially utilized to treat the traumatic injury irrespective of its cause.

## EXAMPLES

[0474] The following examples are intended to provide illustrations of the application of the present invention. The following examples are not intended to completely define or otherwise limit the scope of the invention.

## EXAMPLE 1 - EVALUATION OF COX-1 AND COX-2 ACTIVITY *IN VITRO*

[0475] The COX-2 inhibitors suitable for use in this invention exhibit selective inhibition of COX-1 over COX-2, as measured by $IC_{50}$ values when tested *in vitro* according to the following activity assays.

## PREPARATION OF RECOMBINANT COX BACULOVIRUSES

[0476] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus

transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer ($10^7$-$10^8$ pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0477] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

FAST ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0478] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 µM phenol, 1 µM heme, 300 µM epinephrine) with the addition of 20 µl of 100 µM arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic

acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be utilized as a positive control. The $PGE_2$ formed is typically measured by standard ELISA technology utilizing a PGE2 specific antibody, available from a number of commercial sources.

[0479] Each compound to be tested may be individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular compound. Potency is typically expressed by the $IC_{50}$ value expressed as g compound/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may be determined by the $IC_{50}$ ratio of COX-1/COX-2.

[0480] By way of example, a primary screen may be performed in order to determine particular compounds that inhibit COX-2 at a concentration of 10 ug/ml. The compound may then be subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (e.g., 10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). After this screen, compounds can then be tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. With this assay, the percentage of COX inhibition compared to control can be determined, with a higher percentage indicating a greater degree of COX inhibition. In addition, the $IC_{50}$ value for COX-1 and COX-2 can also be determined for the tested compound. The selectivity for each compound may then be determined by the $IC_{50}$ ratio of COX-1/COX-2, as set-forth above.

EXAMPLE 2

[0481] In the examples below, a combination therapy contains a corticotropin releasing factor antagonist with a vehicle and a COX-2 selective inhibitor. The efficacy of such combination therapy can be evaluated in comparison to a control treatment such as a placebo treatment, administration of a COX-2 inhibitor only, or administration of a corticotropin releasing factor antagonist only. By way of example, a combination therapy may contain $\alpha$-helical CRF 9-41 and celecoxib, $\alpha$-helical CRF 9-41 and valdecoxib, $\alpha$-helical CRF 9-41 and rofecoxib, or $\alpha$-helical CRF 9-41 and paracoxib. In addition, any of the above mentioned COX-2 selective inhibitors may be similarly combined with other CRF antagonists, both peptide and non-peptide, such as for example, the pyrrolopyrimidines disclosed in WO 94/13676, CP-154,526 (Schulz et. al.,

*Proc. Natl. Acad. Sci.* USA, Vol. 93 (1996) 10477-10482), [D-phe$^{12}$,Nle$^{21,38}$]hCRF-(12-14) (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), D-phe CRF (12-14) (Lyons et al. (1991) ), astressin (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), and antalarmin (Webster et al., *Endocrinology*, Vol. 137 (1996) 57475750), NBI 27914 (Chen et al., J Med. Chem. 39: 4358-4360 (1996)), R121919, R121920 (7-dipropylamino)-2,5-dimethyl-3-[2-(dimethylamino)-5-pyridyl] pyrazolo [1,5-a] pyrimidine) (Mackay et al. (2001)), and other CFR antagonists known in the art, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems.

[0482] It should be noted that these are only several examples, and that any CFR antagonist in combination with any COX-2 inhibitor of the present invention may be tested as a combination therapy. The dosages of a CFR antagonist and COX-2 inhibitor in a particular therapeutic combination may be readily determined by a skilled artisan conducting the study. The length of the study treatment will vary on a particular study and can also be determined by one of ordinary skill in the art. The combination therapy may be administered for any time period necessary to treat the ischemic event. By way of example, the combination therapy may be administered for 12 weeks. The CFR antagonist and COX-2 inhibitor can be administered by any route as described herein, but are preferably administered orally or intravenously for human subjects.

[0483] The laboratory animal study can generally be performed as described in Strijbos, et al., (1994) *Brain Research*, 656: 405-408.

[0484] Briefly, the study can be performed on male, Sprague-Dawley rats ranging in size from 200 to 250 g. The rats are anesthetized with sodium pentobarbitone, and guide cannulae are implanted into the third ventricle of the brain. This is performed seven days prior to ischemia. At least four days later, the rats are subjected to a unilateral, permanent middle cerebral artery occlusion ("MCAo") under halothane anesthesia (2% in oxygen) by electrocoagulation according to a modification of the technique disclosed in Tamura et al. ((1981) *J. Cereb. Blood Flow Metab.*, 1: 53-60).Body temperature is maintained during surgery using a heated blanket.

[0485] Rats are then injected with either a vehicle (0.9% saline) or a corticotropin releasing hormone antagonist, such as, for example, $\alpha$-helical CRF 9-41 (6.5 mmol; total volume 2 µl) both 30 minutes before and 10 minutes after the MCAo.

[0486] The brain tissue can then be examined histologically for the effects of combination therapy in comparison to the placebo. Neuronal damage is determined

histologically 24 hours after ischemia. 500 µm coronal brain slices are incubated with tetrazolium stain, a histological indicator of mitochondrial viability. Lesion size is then quantified by automated Seescan image analysis.

EXAMPLE 3

[0487] This laboratory animal study can generally be performed as described in Lyons, et al., (1991) *Brain Research*, 545: 339-342.

[0488] Male Winstar rats weighing 250-300 g are induced with 2.0% halothane, intubates, and ventilated with 1.0% halothane. PE-50 catheters are inserted into the femoral vein and artery, Core body temperature is monitored and maintained at 37.0± 0.5 °C. An intraventricular injection of $\alpha$-helical CRF 9-41 is administered 0.80 mm posterior, 1.50 mm lateral to the bregma and 3.80 mm deep. Fifteen minutes after injection, transient forebrain ischemia is produced for a 10 minute period by the temporary occlusion of both common carotid arteries and phlebotomizing the rat to a MABP of 50 mm Hg. After 10 minutes of ischemia, previously withdrawn and heparinized blood was infused via the femoral venous catheter and cerebral blood flow is restored by removal of the carotid artery clips. Animals are then monitored under 1.0% halothane for a 1 hour period after reperfusion (restoration of carotid blood flow).

[0489] Seven groups of five animals each are studied. Three groups act as control groups: one normal control group, one ischemic control group, and one ischemic vehicle group. The remaining four groups receive $\alpha$-helical CRF 9-41 in doses of 0.1, 1.0, 10.0, or 100.0 µg in 0.9 & BaCl, the volume of each injection being 5 µl. Arterial blood samples are taken and MABP is observed and recorded as follows: 10 minutes prior to injection of $\alpha$-helical CRF 9-41; after 10 minutes of ischemia just prior to reperfusion; and 30 minutes following reperfusion.

[0490] Seven days post-op, each rat is anesthetized with 2.0% halothane and the brain fixed *in situ* with 40% formaldehyde/glacial acetic acid/methanol, 1:1:8 via transcardiac perfusion after briefly washing out the cephalic circulation with heparinized 0.9% NaCl for 45 seconds. The brains are then sectioned 7mm posterior to the rostral tip of the frontal lobes and 10µm paraffin sections are stained using hematoxylin and eosin. Hippocampal regions CA1-medial, CA1-lateral, CA3, and CA4 are examined bilaterally under light microscopy using an ocular grid with magnification X 400. Ten 100 X 100 µm area are analyzed in each hippocampal region. Neurons displaying a normal nucleus, cytoplasmic staining, and configuration are counted as living cells, as

opposed to pyknotic, hyperchromatic, and shrunken neurons that would be counted as dead cells.

[0491] The number of surviving neurons and dead neurons are compared to determine the efficacy of the combination therapy. Furthermore, the $PaCO_2$, $PaO_2$, $pH_a$, MABP, serum glucose, and core body temperatures among the rats representing the various control and experimental groups are compared to determine possible side effects of the therapy or the procedures used.

EXAMPLE 4

[0492] This laboratory animal study can generally be performed as described in Mackay et al., (2001) *J. Cerebral Blood Flow and Metabolism* 21:1208-1214.

[0493] Brain and plasma levels of R121920 are determined in a number of nonoccluded male Sprague–Dawley rats weighing 280 to 340 g. A skilled artisan can readily determine the appropriate number of animals to be used for a particular experiment. R121920 in a vehicle of water is administered to each of the rats as a single intravenous (IV) dose of 10 mg/kg. An equal number of the rats are killed at 2, 5, 15, 30, 60, 120, and 240 minutes subsequent to the administration of R121920. Brains are rapidly removed, flash frozen in liquid nitrogen, and stored at -70°C until analysis. 200 $\mu$L terminal blood samples are collected into tubes containing EDTA and are promptly centrifuged for 1.5 minutes at 10,000 g. The plasma is extracted, flash frozen in liquid nitrogen, and stored at –70°C until analysis. In order to quantify the concentration of R121920 in plasma, 150 $\mu$L acetonitrile is added to 50 $\mu$L plasma to precipitate protein, and the sample is centrifuged. The supernatant is collected and dried in a Speed Vac at room temperature. In order to prepare brain sample tissue, brain tissue is homogenized in 1 mL saline solution. Protein is precipitated by adding 3 vol acetonitrile to the sample solution. After reconstitution, all samples are analyzed in a reverse phase HPLC-UV system. The concentrations of R121920 in the samples is predicted from the linear regression of an external calibration curve of five spiked matrix standards.

[0494] All rats are initially anesthetized with a mixture of 5% halothane, 30% oxygen, and 70% nitrous oxide in an induction chamber and maintained thereafter with a nitrous oxide/oxygen mixture (70%:30%) containing 1.0% to 1.5% halothane administered through a face mask. Body temperature is monitored during the surgical

procedure by a rectal thermometer. The rats are maintained at a normothermic body temperature (37 °C ± 1°C) by use of a heating blanket controlled by the thermometer.

SUBTEMPORAL MIDDLE CEREBRAL ARTERY OCCLUSION MODEL

[0495] Permanent focal ischemia is induced in male Fischer 344 rats (240 to 280 g) through a subtemporal approach, as described in Tamara et al., (1981) *J. Cereb. Blood Flow Metab.* 1: 53-60. Briefly, the craniectomy is performed at the level where the MCA crosses the lateral olfactory tract. The dura is opened, and the artery is exposed and occluded by bipolar diathermy from its origin to the point where it crosses the inferior cerebral vein. All visible lenticulostriate branches are also occluded. The artery is transected to confirm complete occlusion and to prevent recanalization. The incision sites are closed, and the animals are allowed to recover from the anesthesia.

[0496] R121920 (10 mg/kg or 20 mg/kg) is administered as an initial bolus IV dose at the time of the onset of ischemia, followed by subsequent subcutaneous (SC) injections of R121920 (5 mg/kg or 10mg/kg, respectively) at hourly intervals thereafter for a period of 4 hours. Control rats are injected with a water vehicle (1 mL/kg) at the same time points.

[0497] The rats are killed 24 hours subsequent to MCA occlusion, the brains are removed, and 500 $\mu$m coronal sections are cut from the frontal pole on a vibratome. Brain sections are incubated in a 2% solution of triphenyl tetrazolium chloride at 37°C for 30 minutes to stain for viable tissue. Infarcted regions in the hemisphere, the cortex, and the striatum on each of the sections are delineated and transcribed onto scale diagrams and quantified by automated image analysis. The infarct volume for each of the brain regions is computed by summing the areas of damage from each section and multiplying them by the distance between the sections.

INTRALUMINAL SUTURE MIDDLE CEREBRAL ARTERY OCCLUSION MODEL.

[0498] The left middle cerebral artery (MCA) is permanently occluded in a number of male Sprague-Dawley rats weighing 280 to 340 g through a cervical carotid approach using the intraluminal suture technique in male as described in detail in Zea Longa et al., (1989) *Stroke* 20: 84-91. Briefly, the common carotid, the external carotid, and the internal carotid arteries are exposed via a midline cervical incision performed under an operating microscope. A 30-mm length of 3–0 monofilament nylon suture with tip heat-blunted and coated with poly-l-lysine solution (Belayev et al.,(1996) *Stroke* 27:

1616-1622) is advanced from the external carotid artery into the lumen of the internal carotid artery until mild resistance is felt (typically 19 to 20 mm depending upon the body weight of the rat), resulting in the occlusion of the origin of the MCA. After closure of the incision, the rats are allowed to recover from anesthesia.

[0499] R121920 (10 mg/kg) is administered as an IV injection at the time of MCA occlusion, followed by additional IV injections of R121920 (10 mg/kg) at 1, 2, 3 and 4 hours subsequent thereto. Control rats are injected with a water vehicle at the same time points. The period of neuroprotective effect of R121920 is examined by delaying induction of the dosing regimen to 0, 0.5, and 1 hour after occlusion of the MCA.

[0500] Twenty-four hours subsequent to MCA occlusion, the rats are killed and the brains are removed and frozen in isopentane at –40°C. Brains are cut into 20-$\mu$m serial coronal sections at 12 equidistant levels (1 mm apart, covering the entire forebrain), are fixed for 10 minutes in 4% paraformaldehyde, and are stained with hematoxylin and eosin. The sections, corresponding to 12 stereotactically predetermined coronal planes of the brain from anterior +12.7 mm to anterior +1.7 mm relative to the interaural line (Paxinos and Watson, *The rat brain in stereotaxic coordinates*. San Diego, CA: Academic Press), are examined using a light microscope. Areas of ischemic damage are delineated and transcribed onto scale diagrams of a normal forebrain at each of the 12 coronal planes. Infarcted areas are quantified using a computer-based image analysis system, and the total volumes of ischemic tissue for each brain are derived from integration of the areas of damage in the 12 planes and the known stereotactic coordinates of the planes. The volumes of the cerebral hemispheres ipsilateral and contralateral to the occluded MCA are determined from the stained histologic sections by assessment of the total surface area at the same coronal planes as used for assessing areas of ischemic damage. The difference between the two hemispheres provide a measure of brain swelling.

[0501] It should be noted that all of the above-mentioned procedures can be modified for a particular study, depending on factors such as a drug combination used, length of the study, subjects that are selected, etc. Such modifications can be designed by a skilled artisan without undue experimentation.

WHAT IS CLAIMED IS:

1. A method for treating a stroke, the method comprising:

(a) diagnosing a subject in need of treatment for a stroke; and

(b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a corticotropin releasing factor antagonist or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 $IC_{50}$ to COX-2 $IC_{50}$ not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 $IC_{50}$ to COX-2 $IC_{50}$ not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

5. The method of claim 1 wherein the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

6. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered substantially simultaneously.

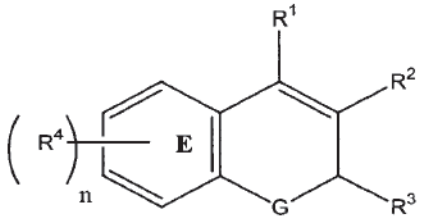
7. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered sequentially.

8. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is administered to the subject in an amount of about 0.1 to about 20 mg/kg body weight per day.

9. The method of claim 1 wherein the corticotropin releasing factor antagonist is administered to the subject in an amount of about 1 to about 50 milligrams per kilogram of the subject's weight per day.

10. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(I)

wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or $NR^a$;

$R^a$ is alkyl;

$R^1$ is selected from the group consisting of H and aryl;

$R^2$ is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

$R^3$ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

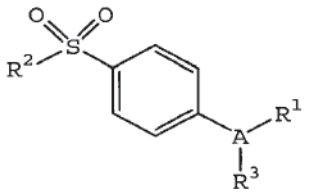
each $R^4$ is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl,

heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or $R^4$ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

11. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof of the formula:



wherein:

A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

$R^1$ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein $R^1$ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

$R^2$ is selected from the group consisting of methyl and amino; and

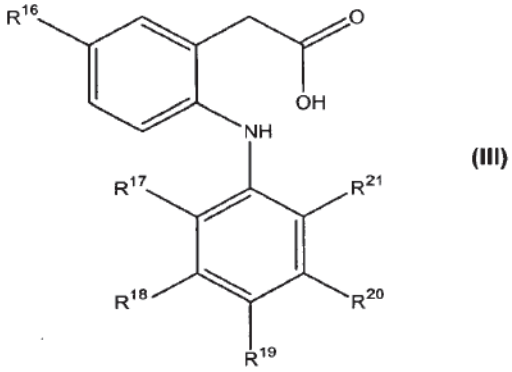
$R^3$ is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl,

alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,
N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

12. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:




(III)

wherein:

$R^{16}$ is methyl or ethyl;

$R^{17}$ is chloro or fluoro;

$R^{18}$ is hydrogen or fluoro;

$R^{19}$ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

$R^{20}$ is hydrogen or fluoro; and

$R^{21}$ is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of $R^{17}$, $R^{18}$, $R^{20}$ and $R^{21}$ is not fluoro when $R^{16}$ is ethyl and $R^{19}$ is H; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

13. A composition comprising a cyclooxygenase-2 selective inhibitor selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

14. The composition of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, and parecoxib, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

pha4279.ST25.txt
SEQUENCE LISTING

<110> Pharmacia Corporation
Arneric, Stephen

<120> COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

<130> PHA 4279. 2 (01572/1/PCT; PC27945A)

<150> US 60/498,148
<151> 2003-08-27

<160> 1

<170> PatentIn version 3.1

<210> 1
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<223> alpha-helical CRF 9-41
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1 5 10 15

Gln Ala Glu Gln Ala Leu Asn Arg Leu Leu Glu Xaa
20 25

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1612 |
| Serial Number: | 18/307,718 | Examiner: | RONEY, CELESTE A |
| Filing or 371 (c) Date: | 2023-04-26 | **CONFIRMATION NO:** | **9067** |
| Title: | CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS | | |

**FILED ELECTRONICALLY ON: July 12, 2024**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $260.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.50535-709.307).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: July 12, 2024

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| 18/307,718 | 07/12/2024 05:38:22 PM Z ET | 50535-709.307 |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Kaia Parenti |
| PATENT CENTER # | 66348141 | AUTHORIZED BY | - |
| CUSTOMER # | 21971 | FILING DATE | 04/26/2023 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| DA / 232415 | E20247BH38525222 | Kaia Parenti |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1464 | PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III) | 140.00 | 1 | 140.00 |
| 1801 | REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114) | 1360.00 | 1 | 1360.00 |
| | | | TOTAL AMOUNT: | $1,500.00 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

## PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 49001 | (congenital adj2 adrenal adj2 hyperplasia) AND (CRF adj2 receptor adj2 antagonist) AND (stability OR stable) AND (ACTH)(hydroxyprogesterone) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/07/23 10:24 AM |
| L2 | 49000 | (congenital adj2 adrenal adj2 hyperplasia) WITH (CRF adj2 receptor adj2 antagonist) AND (stability OR stable) AND (ACTH)(hydroxyprogesterone) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/07/23 10:24 AM |
| L3 | 15 | (congenital adj2 adrenal adj2 hyperplasia) WITH (CRF adj2 receptor adj2 antagonist) AND (stability OR stable) AND (ACTH) AND (hydroxyprogesterone) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2024/07/23 10:24 AM |
| L4 | 14 | L3 AND ( (A61K31/519 OR A61K31/4245 OR A61K31/427 OR | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, | OR | ON | ON | 2024/07/23 10:25 AM |

| | | | | | | | |
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| | | A61K31/4985 OR A61K31/5377 OR A61K45/06 OR A61K9/0053 OR A61K9/20 OR A61K9/2004 OR A61K9/48 OR A61K9/4841 OR A61P5/38 OR A61P35/00 OR A61P5/06 OR A61P5/08 OR A61P5/00 OR A61P5/24).cpc.) | CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L5 | 26 | ((("SPRUCE") near3 ("BIOSCIENCES") near3 ("INC"))).AS,AANM. | (US-PGPUB; USPAT) | OR | ON | ON | 2024/07/23 10:28 AM |
| L6 | 210 | ((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal")) OR (("HUANG") near3 ("Michael"))).INV. | (US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT) | OR | ON | ON | 2024/07/23 10:28 AM |

## PE2E SEARCH - Search History (Interference)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| N1 | 0 | L3 AND ( (A61K31/519 OR A61K31/4245 OR A61K31/427 OR A61K31/4985 OR A61K31/5377 OR A61K45/06 OR A61K9/0053 OR A61K9/20 OR A61K9/2004 OR A61K9/48 OR A61K9/4841 OR A61P5/38 OR A61P35/00 OR A61P5/06 OR A61P5/08 OR A61P5/00 OR A61P5/24).cpc.) | (US-PGPUB; USPAT) | OR | ON | ON | 2024/07/23 10:25 AM |

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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# NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 08/07/2024

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| RONEY, CELESTE A | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 08/07/2024

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $1200.00 | $0 | 11/07/2024 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.**

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 08/07/2024
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

| (Typed or printed name) |
|---|
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $1200.00 | $0 | 11/07/2024 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| RONEY, CELESTE A | 1612 | 424-489000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____



PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

21971 7590 08/07/2024

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| RONEY, CELESTE A | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 08/07/2024

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

| Notice of Allowability | Application No. 18/307,718 | Applicant(s) HOWERTON et al. | |
|---|---|---|---|
| | Examiner CELESTE A RONEY | Art Unit 1612 | AIA (FITF) Status Yes |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to IDS, filed 7/12/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-15 and 17-22 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 7/12/24.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Victoria Cheng on 07/26/2024.

The application has been amended as follows:

1. Claim 1, at lines 10, 11 and 13, the word [subject] has been deleted and replaced with the word ---human---, at each instance of occurrence.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached Monday-Friday; 8 AM-6 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

# Web Search History

| date, time | web site | search string |
|---|---|---|
| 7/23/2024 10:20:56 AM | Google Patents | Search Term 1<br>(congenital-adrenal-hyperplasia)(CRF-receptor-antagonist) (stability, stable)(ACTH)(hydroxyprogesterone)) |
| 7/23/2024 10:21:07 AM | Google Patents | Search Term 1<br>(congenital-adrenal-hyperplasia)(CRF-receptor-antagonist) (stability, stable)(ACTH)(hydroxyprogesterone) |
| 7/23/2024 10:21:45 AM | Google Scholar | (congenital-adrenal-hyperplasia)(CRF-receptor-antagonist) (stability, stable)(ACTH)(hydroxyprogesterone) |

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | CELESTE A RONEY | 1612 |

| CPC | | | | | | |
|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Version** |
| A61K | / | 31 | / | 5377 | F | 2013-01-01 |
| A61P | / | 5 | / | 24 | I | 2018-01-01 |
| A61K | / | 9 | / | 14 | I | 2013-01-01 |
| A61K | / | 9 | / | 48 | I | 2013-01-01 |
| C07D | / | 487 | / | 04 | I | 2013-01-01 |
| A61K | / | 31 | / | 573 | I | 2013-01-01 |
| A61P | / | 5 | / | 00 | I | 2018-01-01 |
| A61P | / | 5 | / | 38 | I | 2018-01-01 |
| A61K | / | 9 | / | 4825 | I | 2013-01-01 |

| CPC Combination Sets | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Set** | **Ranking** | **Version** |
| A61K | / | 31 | / | 5377 | I | 1 | 1 | 2013-01-01 |
| A61K | / | 2300 | / | 00 | I | 1 | 2 | 2013-01-01 |
| A61K | / | 31 | / | 573 | I | 2 | 1 | 2013-01-01 |
| A61K | / | 2300 | / | 00 | I | 2 | 2 | 2013-01-01 |

| NONE | | **Total Claims Allowed:** | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | 23 July 2024 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | none |

U.S. Patent and Trademark Office — Part of Paper No.: 20240723

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | CELESTE A RONEY | 1612 |

| INTERNATIONAL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|
| **CLAIMED** | | | | | |
| A61K31/5377 | / | 31 | / | 5377 | |
| A61P5/00 | / | 5 | / | 00 | |
| C07D487/04 | / | 487 | / | 04 | |

| NON-CLAIMED | | | | |
|---|---|---|---|---|
| | / | | / | |

| US ORIGINAL CLASSIFICATION | |
|---|---|
| **CLASS** | **SUBCLASS** |
| | |

| CROSS REFERENCES(S) | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **SUBCLASS (ONE SUBCLASS PER BLOCK)** | | | | | |
| | | | | | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | 23 July 2024 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | none |

U.S. Patent and Trademark Office — Part of Paper No.: 20240723

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | CELESTE A RONEY | 1612 |

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

**CLAIMS**

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 10 | 10 | 19 | 20 | | | | | | | | | | |
| 2 | 2 | 11 | 11 | 20 | 21 | | | | | | | | | | |
| 3 | 3 | 12 | 12 | 21 | 22 | | | | | | | | | | |
| 4 | 4 | 13 | 13 | | | | | | | | | | | | |
| 5 | 5 | 14 | 14 | | | | | | | | | | | | |
| 6 | 6 | 15 | 15 | | | | | | | | | | | | |
| 7 | 7 | 16 | 17 | | | | | | | | | | | | |
| 8 | 8 | 17 | 18 | | | | | | | | | | | | |
| 9 | 9 | 18 | 19 | | | | | | | | | | | | |

| | | | |
|---|---|---|---|
| NONE | | **Total Claims Allowed:** | |
| (Assistant Examiner) | (Date) | 21 | |
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | 23 July 2024 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | none |

U.S. Patent and Trademark Office Part of Paper No.: 20240723

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | Examiner | Art Unit |
| | CELESTE A RONEY | 1612 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61K31/5377; A61P5/38; A61P5/00; A61P5/24; A61K9/14; A61K9/48; A61K9/4825; A61K31/573; C07D487/04 further limited by CAH and CRF1 receptor antagonist and glucocorticoid and baseline and reduced | 10/04/2023 | CR |
| A61K31/5377; A61P5/38; A61P5/00; A61P5/24; A61K9/14; A61K9/48; A61K9/4825; A61K31/573; C07D487/04 further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| A61K31/5377; A61P5/38; A61P5/00; A61P5/24; A61K9/14; A61K9/48; A61K9/4825; A61K31/573; C07D487/04 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | |
|---|---|

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/307,718 | HOWERTON et al. |
| | Examiner | Art Unit |
| | CELESTE A RONEY | 1612 |

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| palm inventor search. google (patents and scholar) and PE2E searches further limited by CAH and CRF1 receptor antagonist and glucocorticoid and baseline and reduced | 10/04/2023 | CR |
| palm inventor search. google (patents and scholar) and PE2E searches further limited by CAH and CRF1 receptor antagonist and stab$5 | 02/07/2024 | CR |
| palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by CAH and CRF1 receptor antagonist and stab$5 and ACTH and hydroxyprogesterone | 07/23/2024 | CR |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| A61K31 | 5377 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61P5 | 38 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61P5 | 00 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61P5 | 24 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61K9 | 14 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61K9 | 48 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61K9 | 4825 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| A61K31 | 573 further limited by CAH and CRF1 receptor antagonist and stab$5 | 07/23/2024 | CR |
| C07D487 | 04 further limited by CAH and CRF1 receptor antagonist and stab$5 and aCTH and hydroxyprogesterone | 07/23/2024 | CR |

| | |
|---|---|
| /CELESTE A RONEY/<br>Primary Examiner, Art Unit 1612 | |

# Bibliographic Data

Application No: 18/307,718

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /CELESTE A RONEY/ Examiner's Signature | Initials

Title: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

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| FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 04/26/2023 | 424 | 1612 | 50535-709.307 |
| RULE | | | |

**APPLICANTS**

Spruce Biosciences, Inc., South San Francisco, CA, UNITED STATES

**INVENTORS**

Alexis HOWERTON,

Hal GERBER,

Michael HUANG,

**CONTINUING DATA**

This application is a CON of 18078649 12/09/2022

18078649 is a CON of 17586228 01/27/2022ABN

17586228 is a DIV of 17359411 06/25/2021 PAT 11351177

17359411 is a CON of 17063592 10/05/2020 PAT 11344557

17063592 is a CON of 16388620 04/18/2019 PAT 10849908

16388620 is a CON of PCT/US2018/046760 08/14/2018

PCT/US2018/046760 has PRO of 62545406 08/14/2017

**FOREIGN APPLICATIONS**

**IF REQUIRED, FOREIGN LICENSE GRANTED****

09/18/2023

**STATE OR COUNTRY**

**ADDRESS**

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050
UNITED STATES

**FILING FEE RECEIVED**

$6,260

Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-20110136865 | 06-09-2011 | BUNTINX; Erik | |
| | 002 | US-20220133742 | 05-05-2022 | GHOSH; Sangita et al. | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | 001 | CN-101516835-A | 08-26-2009 | OSURF OHIO STATE UNIVERSITY RE [US] | Abstract: | ☒ |
| | 002 | WO-2005020910-A2 | 03-10-2005 | PHARMACIA CORP [US], et al. | | ☐ |
| | 003 | WO-2013160317-A2 | 10-31-2013 | HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE] | | ☐ |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 07/23/2024 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

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Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | DO, Hien-Quang et. al; Copper-catalyzed arylation of C-H bonds; Abstracts of Papers, 236th ACS National Meeting, New Orleans, LA, Apr. 6-10, 2008, Accession No. 2008:390596. | ☐ |
| | 002 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review of U.S. Patent No. 11,007,201 dated December 1, 2023 (pp. 1-38) (PGR2022-00025). | ☐ |
| | 003 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 10,849,908 dated May 28, 2021 (pp. 1-90) (PGR2021-00088). | ☐ |
| | 004 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 11,007,201 dated February 18, 2022 (pp 1-92) (PGR2022-00025). | ☐ |
| | 005 | U.S. Serial No. 16/639,541 Office Action dated April 4, 2022. | ☐ |
| | 006 | U.S. Serial No. 17/586,228 Office Action dated March 30, 2022. | ☐ |

| Examiner Signature | /CELESTE A RONEY/ | Date Considered | 07/23/2024 |
|---|---|---|---|

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 4

| Complete if Known | |
|---|---|
| Application Number | 18/307,718 |
| Filing Date | 04-26-2023 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1612 |
| Examiner Name | RONEY, CELESTE A |
| Attorney Docket Number | 50535-709.307 |

## CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2024-07-12 |
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

/CELESTE A RONEY/ 07/23/2024

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The information provided by you in this form will be subject to the following routine uses:

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

/CELESTE A RONEY/ 07/23/2024

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Commissioner for Patents
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Alexandria, Virginia 22313-1450

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21971 7590 08/07/2024
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PALO ALTO, CA 94304-1050

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| | |
|---|---|
| Jennifer Vail | (Typed or printed name) |
| /jvail/ | (Signature) |
| 8/13/2024 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $1200.00 | $0 | 11/07/2024 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| RONEY, CELESTE A | 1612 | 424-489000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 WILSON SONSINI GOODRICH & ROSATI
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SPRUCE BIOSCIENCES, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): South San Francisco, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☑ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

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☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Kaia R. Parenti/ Date August 13, 2024

Typed or printed name Kaia R. Parenti Registration No. 81050



PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/307,718** | **08/13/2024 01:56:56 PM Z ET** | **50535-709.307** |

## Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9067 | FILED BY | Jennifer Vail |
| PATENT CENTER # | 66764028 | FILING DATE | 04/26/2023 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Kaia Parenti |

## Documents

**TOTAL DOCUMENTS: 1**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| Spruce_50535-709_307_IssueFeeTransmittal.pdf | 1 | Issue Fee Payment (PTO-85B) | 131 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce_50535-709_307_IssueFeeTransmittal.pdf | 76D3409A09C7CA0ED2E53F76225F9173EDE5684D10C37E430017E342DD6740F1C72880488CE24A8627A351244551F919CFBA08131A589D632CEF45E28C0AA4CF |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

## PART B - FEE(S) TRANSMITTAL

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**Certificate of Mailing or Transmission**

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| | |
|---|---|
| Jennifer Vail | (Typed or printed name) |
| /jvail/ | (Signature) |
| 8/13/2024 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 04/26/2023 | Alexis HOWERTON | 50535-709.307 | 9067 |

TITLE OF INVENTION: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $1200.00 | $0 | 11/07/2024 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| RONEY, CELESTE A | 1612 | 424-489000 |

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☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 WILSON SONSINI GOODRICH & ROSATI
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: **SPRUCE BIOSCIENCES, INC.**

(B) RESIDENCE: (CITY and STATE OR COUNTRY): **South San Francisco, California**

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☑ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

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Authorized Signature /Kaia R. Parenti/ Date August 13, 2024

Typed or printed name Kaia R. Parenti Registration No. 81050



PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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*Office of the Chief Financial Officer*

Document Code:WFEE

User :Cynthia Chau

Sale Adjustment Accounting Date:08/14/2024

| Effective Date | Sale Accounting Date | Sale Item Reference Number |
|---|---|---|
| 08/14/2024 | 08/14/2024 | 18307718 |

| Document Number | Fee Code | Fee Code Description | Amount Paid | Payment Method |
|---|---|---|---|---|
| I20248D944195102 | 1501 | UTILITY APPL ISSUE FEE | $1,200.00 | DA |

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| I20248D944195102 | 1501 | UTILITY APPL ISSUE FEE | $1,200.00 | DA | 232415 |

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| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/307,718 | 10/15/2024 | 12115166 | 50535-709.307 | 9067 |

21971 7590 09/25/2024

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

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# EGRANT NOTIFICATION

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