

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
 UNDER 37 CFR 1.102(e) (Page 1 of 1)**

First Named Inventor:	Joseph K. Belanoff	Nonprovisional Application Number (if known):	
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.
2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
 ---OR---
 (b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- i. A request for continued examination has been filed with, or prior to, this form.
- ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
- iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Yifan Mao/	Date June 19, 2017
Name (Print/Typed) Yifan Mao	Practitioner Registration Number 60,804

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 1 forms are submitted.

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.

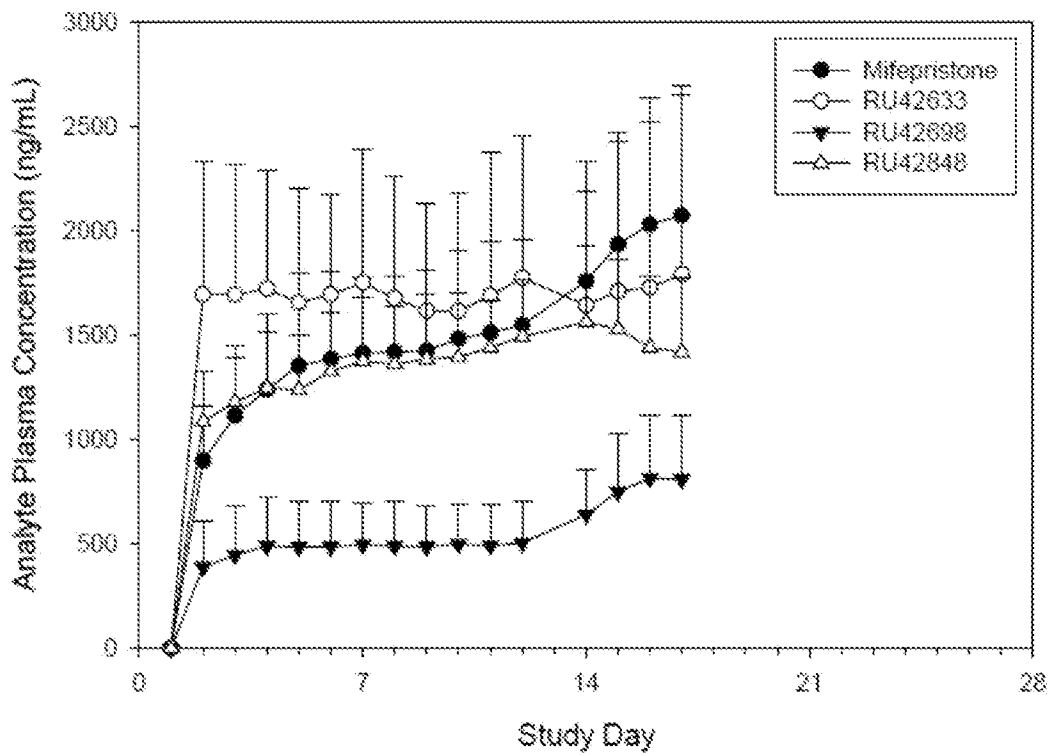


FIG. 1

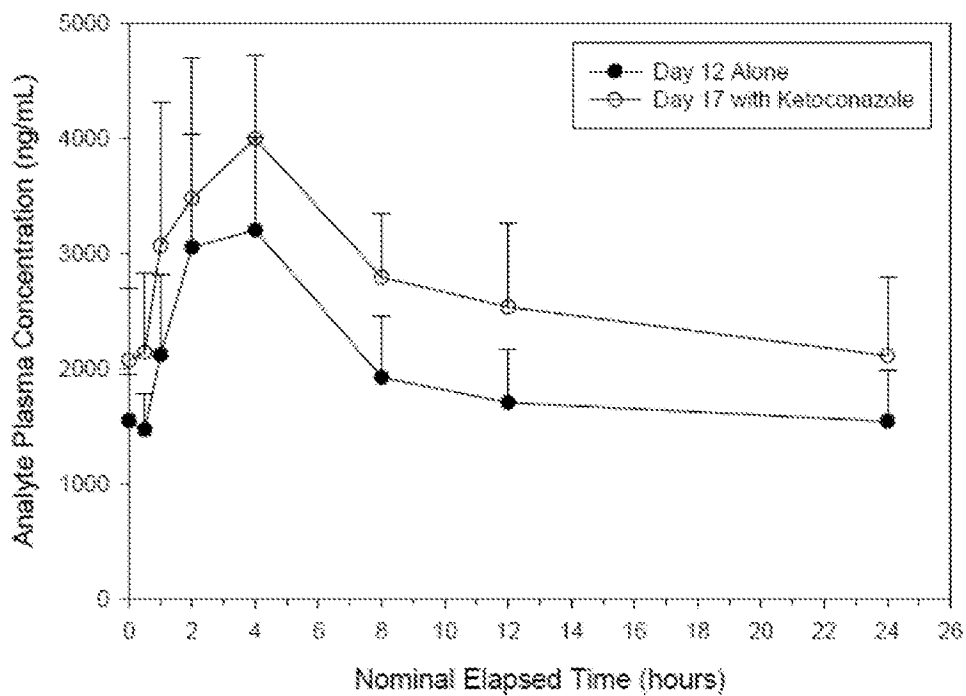


FIG. 2

ABSTRACT

CONCOMITANT ADMINISTRATION of GLUCOCORTICOID RECEPTOR MODULATORS and CYP3A INHIBITORS

Applicant provides methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of a glucocorticoid receptor antagonist (GRA) and steroidogenesis inhibitors, and by concomitant administration of a GRA and CYP3A inhibitors. Applicant provides methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of mifepristone and ketoconazole.

Subjects treated with CYP3A inhibitors or steroidogenesis inhibitors may suffer from toxicity or other serious adverse reactions; concomitant administration of other drugs would be expected to increase the risk of such toxicity and adverse reactions. Applicant has surprisingly found that GRAs may be administered to subjects receiving CYP3A inhibitors or steroidogenesis inhibitors such as ketoconazole without increasing risk adverse reactions; for example, Applicant has found that mifepristone may be concomitantly administered with ketoconazole (a CYP3A inhibitor and a steroidogenesis inhibitor), providing safe concomitant administration of the GRA and ketoconazole. In embodiments, the GRA dose may be reduced.

CLAIMS

1. A method of treating Cushing's syndrome in a patient who is taking a glucocorticoid receptor antagonist (GRA) comprising reducing the daily dose of said GRA from an original dose to an adjusted dose that is at least 33% less than said original dose when the patient is receiving concomitant administration of a CYP3A inhibitor.
2. The method of claim 1, wherein said original dose is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted dose is 600 mg per day of said GRA.
3. The method of claim 1, wherein said original dose is 600 milligrams (mg) per day of said GRA, and said adjusted dose is 300 mg per day of said GRA, further comprising titrating the adjusted dose to a maximum of 600 mg per day of said GRA.
4. The method of claim 1, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
5. The method of claim 2, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
6. The method of claim 3, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
7. The method of claim 1, wherein said CYP3A inhibitor is ketoconazole.
8. The method of claim 4, wherein said CYP3A inhibitor is ketoconazole.
9. The method of claim 5, wherein said CYP3A inhibitor is ketoconazole.
10. A method of treating symptoms associated with elevated cortisol levels in a patient who is taking a glucocorticoid receptor antagonist (GRA) comprising reducing the daily dose of said GRA from an original dose to an adjusted dose that is at least 33% less than said original dose when the patient is receiving concomitant administration of a CYP3A inhibitor.
11. The method of claim 10, wherein said original dose is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted dose of GRA is 600 mg per day of said GRA.
12. The method of claim 10, wherein said original dose is 600 milligrams (mg) per day of said GRA, and said adjusted dose is 300 mg per day of said GRA, further comprising titrating the adjusted dose to a maximum of 600 mg per day of said GRA.

13. The method of claim 10, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
14. The method of claim 11, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
15. The method of claim 12, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
16. The method of claim 10, wherein said CYP3A inhibitor is ketoconazole.
17. The method of claim 13, wherein said CYP3A inhibitor is ketoconazole.
18. The method of claim 14, wherein said CYP3A inhibitor is ketoconazole.
19. A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking a glucocorticoid receptor antagonist (GRA) comprising reducing the daily dose of said GRA from an original dose to an adjusted dose that is at least 33% less than said original dose when the patient is receiving concomitant administration of a CYP3A inhibitor.
20. The method of claim 19, wherein said original dose is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted dose of GRA is 600 mg per day of said GRA.
21. The method of claim 19, wherein said original dose is 600 milligrams (mg) per day of said GRA, and said adjusted dose is 300 mg per day of said GRA, further comprising titrating the adjusted dose to a maximum of 600 mg per day of said GRA.
22. The method of claim 19, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
23. The method of claim 20, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
24. The method of claim 21, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.
25. The method of claim 19, wherein said CYP3A inhibitor is ketoconazole.
26. The method of claim 22, wherein said CYP3A inhibitor is ketoconazole.
27. The method of claim 23, wherein said CYP3A inhibitor is ketoconazole.

28. A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome comprising administering a daily dose of 600 milligrams (mg) mifepristone when the patient is receiving concomitant administration of a CYP3A inhibitor.
29. The method of claim 28, wherein the CYP3A inhibitor is ketoconazole.
30. The method of claim 29, wherein said daily dose of mifepristone is titrated up to 600 mg per day from 300 mg per day.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
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As the below named inventor, I hereby declare that:

This declaration

is directed to:

The attached application, or

United States application or PCT international application number

filed on

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

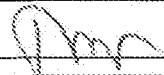
WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Joseph K. Belanoff

Date (Optional): 6/16/17

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.

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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	085178-1053027-011410US
		Application Number	
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Joseph	K.	Belanoff		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Menlo Park	State/Province	CA	Country of Residence	US
Mailing Address of Inventor:					
Address 1	c/o Corcept Therapeutics, Inc.				
Address 2	149 Commonwealth Drive				
City	Menlo Park	State/Province	CA		
Postal Code	94025	Country	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.					Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
<input type="checkbox"/> An Address is being provided for the correspondence information of this application.			
Customer Number	144579		
Email Address	pefiling@kilpatricktownsend.com	Add Email	Remove Email

Application Information:

Title of the Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS		
Attorney Docket Number	085178-1053027-011410US	Small Entity Status Claimed	<input checked="" type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085178-1053027-011410US
	Application Number	
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

Request Early Publication (Fee required at time of Request 37 CFR 1.219)

Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	144579		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		<input type="button" value="Remove"/>
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62465772	2017-03-01

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	085178-1053027-011410US	
		Application Number		
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS			
Prior Application Status	Pending			<input type="button" value="Remove"/>
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
	Claims benefit of provisional	62466867	2017-03-03	
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			<input type="button" value="Remove"/>
Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			<input type="button" value="Add"/>

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085178-1053027-011410US
	Application Number	
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085178-1053027-011410US
	Application Number	
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	<input type="button" value="Remove"/>
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p>		
<input type="button" value="Clear"/>		
<input checked="" type="radio"/> Assignee	<input type="radio"/> Legal Representative under 35 U.S.C. 117	<input type="radio"/> Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
<div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
Name of the Deceased or Legally Incapacitated Inventor: <input type="text"/>		
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>		
Organization Name	<input type="text" value="Corcept Therapeutics, Inc."/>	
Mailing Address Information For Applicant:		
Address 1	<input type="text" value="149 Commonwealth Drive"/>	
Address 2	<input type="text"/>	
City	<input type="text" value="Menlo Park"/>	State/Province <input type="text" value="CA"/>
Country	<input type="text" value="US"/>	Postal Code <input type="text" value="94025"/>
Phone Number	<input type="text"/>	Fax Number <input type="text"/>
Email Address	<input type="text"/>	
Additional Applicant Data may be generated within this form by selecting the Add button. <input type="button" value="Add"/>		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085178-1053027-011410US
	Application Number	
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS	

Assignee	1
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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here.

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1				
Address 2				
City		State/Province		
Country ⁱ		Postal Code		
Phone Number		Fax Number		
Email Address				

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Yifan Mao/		Date (YYYY-MM-DD)	2017-06-19	
First Name	Yifan	Last Name	Mao	Registration Number	60,804

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085178-1053027-011410US
	Application Number	
Title of Invention	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		
	Filing Date		herewith
	First Named Inventor	Joseph K. Belanoff	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		085178-1053027-011410US

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	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 ⁵
	A1.	CASTINETTI et al., "Ketoconazole in Cushing's Disease: Is It Worth a Try?", J Clin Endocrinol Metab, May 2014, 99(5):1623-1630	
	A2.	FLESERIU et al., "Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome", J Clin Endocrinol Metab, June 2012, 97(6):2039-2049	
	A3.	GAL et al., "Effect of ketoconazole on steroidogenic human granulosa-luteal cells in culture", European Journal of Obstetrics & Gynecology and Reproductive Biology, (1991) 39:209-214	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number			
	Filing Date		herewith	
	First Named Inventor	Joseph K. Belanoff		
	Art Unit			
	Examiner Name			
	Attorney Docket Number		085178-1053027-011410US	

	A4.	LATRILLE et al., "A Comparative Study of the Effects of Ketoconazole and Fluconazole on 17-β Estradiol Production by Rat Ovaries in Vitro", Research Communications in Chemical Pathology and Pharmacology, (April 1989), 64(1):173-177	
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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			
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PATENT
Atty. Docket No.: 085178-1053027-011410US

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara
Jo Ann Honcik Dallara

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: not yet known

Filed: (herewith)

For: CONCOMITANT

ADMINISTRATION OF
GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A
INHIBITORS

Customer No.: 144579

Confirmation No.: not yet known

Examiner: not yet known

Technology Center/Art Unit: not yet known

INFORMATION DISCLOSURE
STATEMENT

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

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no

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This IDS is being filed before the mailing date of the first Office Action on the merits.

Applicant believes that no fee is required for submission of this statement. However, if any additional fees are due for the submission of this Information Disclosure Statement, please deduct those fees from Deposit Account No. 20-1430.

Respectfully submitted,

/Yifan Mao/

Yifan Mao
Registration No. 60,804

KILPATRICK TOWNSEND & STOCKTON LLP

Attachment

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS			
First Named Inventor/Applicant Name:	Joseph K. Belanoff			
Filer:	Yifan Mao/Jo Ann Honcik Dallara			
Attorney Docket Number:	085178-1053027-011410US			
Filed as Small Entity				
Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	70	70
UTILITY SEARCH FEE	2111	1	300	300
UTILITY EXAMINATION FEE	2311	1	360	360
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	2202	10	40	400
INDEPENDENT CLAIMS IN EXCESS OF 3	2201	1	210	210

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous-Filing:				
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				3410

Electronic Acknowledgement Receipt

EFS ID:	29543906
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Yifan Mao/Jo Ann Honcik Dallara
Filer Authorized By:	Yifan Mao
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	19-JUN-2017
Filing Date:	
Time Stamp:	21:13:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$3410
RAM confirmation Number	062017INTEFSW21142500
Deposit Account	201430
Authorized User	Jennifer Jacobs

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	Track1sb0424.PDF	141255	no	2
			f1db2172f2f55b8dccc6cb12574c7b0a07bbd237		

Warnings:

Information:

2		SpecClmsAbstDwgs1053027-011410US_600mg.pdf	699196	yes	98
			f882754f16ff808958db9b40a3488ca7c9abf2e1		

Multipart Description/PDF files in .zip description

Document Description	Start	End
Drawings-only black and white line drawings	98	98
Specification	94	97
Abstract	93	93
Claims	90	92
Specification	1	89

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Information:

3	Oath or Declaration filed	Signed_Declaration_Belanoff_CYP3A_600.pdf	437545	no	1
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Warnings:

Information:

4	Application Data Sheet	ADSaia0014.PDF	1823208	no	8
			6ab3ec1c5a2239e7152c0c8430ae126c32700468		

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Information:

5		IDS1.pdf	169465	yes	4
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Multipart Description/PDF files in .zip description					
Document Description			Start	End	
Information Disclosure Statement (IDS) Form (SB08)			3	4	
Transmittal Letter			1	2	
Warnings:					
Information:					
6	Non Patent Literature	A1_NPL_Casinetti_2014.pdf	867121	no	8
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Warnings:					
Information:					
7	Non Patent Literature	A2_NPL_Fleseriu_2012.pdf	1069951	no	11
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Warnings:					
Information:					
8	Non Patent Literature	A3_NPL_Gal_1991.pdf	594653	no	6
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Warnings:					
Information:					
9	Non Patent Literature	A4_NPL_Latrilie_1989.pdf	937902	no	5
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10	Fee Worksheet (SB06)	fee-info.pdf	43182	no	2
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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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NON-PROVISIONAL PATENT APPLICATION

**CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A INHIBITORS.**

Inventor:

Joseph K. Belanoff, residing at Menlo Park, CA 94025

Applicant: Corcept Therapeutics, Inc. 149 Commonwealth Drive Menlo Park, CA 94025

Assignee: Corcept Therapeutics, Inc. 149 Commonwealth Drive Menlo Park, CA 94025

Entity: Small

KILPATRICK TOWNSEND & STOCKTON LLP

CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Application Serial No. 62/465,772, filed March 1, 2017, and U.S. Provisional Application Serial No. 62/466,867, filed March 3, 2017, the entire contents of both of which applications are hereby incorporated by reference in their entireties.

BACKGROUND

[0002] Steroid molecules, such as steroid hormones, play an important role in bodily functions and in bodily responses to infectious and other diseases, and to the environment. Many steroid molecules are synthesized in the body, or are produced from molecules consumed in the diet. Steroid molecules which act as hormones in the body include estrogen, progesterone, testosterone, and cortisol. Some steroid molecules have medicinal effects. Inhibition of steroid synthesis or metabolism can be useful in the treatment of some disorders.

[0003] Cortisol, a steroid molecule, plays an important role in many bodily functions. Cortisol exerts effects by binding to cortisol receptors, which are present in most tissues in the body. However, dysregulation of cortisol may have adverse effects on a subject. For example, Cushing's syndrome, caused by excess levels of cortisol, is characterized by symptoms including elevated blood pressure, elevated blood glucose, increased weight, increased mid-section perimeter, other pre-diabetic symptom, a "moon-face" facial appearance, immune suppression, thin skin, acne, depression, hirsutism, and other symptoms. Clinical manifestations of Cushing's syndrome include abnormalities in glucose control, requirement for anti-diabetic medication, abnormalities in insulin level, abnormal psychiatric symptoms, cushingoid appearance, acne, hirsutism, and increased or excessive body weight, and other symptoms.

[0004] One effective treatment of cortisol dysregulation is to block the binding of cortisol to cortisol receptors, or to block the effect of cortisol binding to cortisol receptors. Mifepristone binds to cortisol receptors, and acts to block such binding and to block the effect of cortisol on

tissues. Mifepristone is 11 β -(4-dimethylaminophenyl)-17 β -hydroxy-17 α -(1-propynyl)-estra-4,9-dien-3-one).

[0005] Another effective treatment of cortisol dysregulation is to reduce the synthesis of cortisol, e.g., by reducing or blocking steroid synthesis. A “steroidogenesis inhibitor” is a compound which reduces or blocks the synthesis of steroid molecules (including, e.g., cortisol) when administered to a subject. Steroidogenesis inhibitors include, for example, ketoconazole, metyrapone, etomidate, and other drugs.

[0006] Many enzymes are involved in steroid synthesis and in steroid metabolism, including cytochrome P450 enzymes, encoded by CYP genes. Inhibiting steroid synthesis may lower the levels of steroids, including, e.g., cortisol, in the blood. For example, CYP3A enzymes play important roles in the synthesis of steroid hormones such as cortisol.

[0007] However, many drugs inhibit the levels or actions of CYP3A gene products (termed “inhibit CYP3A”). The following drugs inhibit CYP3A: ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole, among many drugs which inhibit CYP3A. For example, the following drugs strongly inhibit CYP3A (i.e., increase AUC (area under the concentration-time curve) by 10-fold or greater of sensitive index substrates), either alone or in combination with other drugs: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir, ritonavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole,, saquinavir, telaprevir, tipranavir, troleandomycin, and voriconazole.

[0008] Ketoconazole is an exemplary and an important steroidogenesis inhibitor and is a strong CYP3A inhibitor. Ketoconazole (chemical name: 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine) is administered for the treatment of fungal infections; it also affects steroid metabolism by inhibiting steroidogenesis, and has anti-glucocorticoid and anti-androgen effects due to its interference with enzymatic conversion of cholesterol to hormones such as cortisol and testosterone. Ketoconazole has effects on liver enzymes and the gastrointestinal (GI) tract, among other effects (Fleseriu and Castinetti, *Pituitary* 19:643-653 (2016)).

[0009] Ketoconazole inhibits steroid synthesis and is thus useful in the treatment of Cushing's syndrome; in the treatment of prostate cancer and other androgen-sensitive cancers; to reduce estrogen or progesterone production (e.g., in patients with hormone-sensitive cancers such as breast cancer and ovarian cancer); and in other treatments.

[0010] A drug such as ketoconazole is typically metabolized and excreted by a subject over time following administration. An effective dose is determined based on the expected amounts of metabolism and excretion of the drug. Changes in the amounts or rates of metabolism and/or excretion of a drug will affect the dose required, and may make an otherwise safe dose, if metabolism or excretion changes, into either a less, or ineffective dose, or a more effective or even toxic dose.

[0011] However, although sometimes clinically useful, ketoconazole may have adverse, including seriously toxic, effects (Fleseriu and Castinetti, *Pituitary* **19**:643-653 (2016)). The U.S. Food and Drug Administration issued a Drug Safety Communication (July 26, 2013 Safety Announcement regarding Nizoral® (ketoconazole)) warning of potentially fatal liver damage associated with oral ketoconazole treatment and warning of the risk of adrenal insufficiency, also a potentially fatal disorder. The Safety Announcement warned: "Nizoral tablets can cause liver injury, which may potentially result in liver transplantation or death." The Safety Announcement further stated: "Nizoral tablets may interact with other drugs a patient is taking and can result in serious and potentially life-threatening outcomes, such as heart rhythm problems." Thus, ketoconazole can be quite toxic if administered in excessive amounts, or if it is administered to sensitive individuals, particularly when administered systemically (as opposed, e.g., to topically). This toxicity can lead to liver damage (sometimes requiring liver transplantation). Other CYP3A inhibitors, including, e.g., itraconazole, ritonavir, and other CYP3A inhibitors as discussed herein, may have similar effects and may require similar warnings.

[0012] The simultaneous, or nearly simultaneous (e.g., concomitant) presence of two drugs in a subject may alter the effects of one or the other, or both, drugs. Such alterations are termed drug-drug interactions. For example, the required dose of a drug is often strongly affected by taking the amount and rate of its degradation in, and elimination from, the body (e.g., by liver or kidney action). However, the presence of a second drug in the body, which is also being acted upon by the liver and kidney, can have significant effects on the amount and rate of degradation of the first drug, and can increase the amount of the first drug that remains in the body at a given

time beyond the amount that would have been present at that time in the absence of the second drug. Thus, the presence of a second drug can often increase the effective dose of the first drug. Where the first drug has toxic side effects, such an increase in effective dose of the first drug may lead to dangerous toxicity that would not have been expected were the second drug not present.

[0013] Concomitant administration of different drugs often leads to adverse effects since the metabolism and/or excretion of each drug may reduce or interfere with the metabolism and/or excretion of the other drug(s), thus increasing the effective concentrations of those drugs as compared to the effective concentrations of those drugs when administered alone. Thus, concomitant administration of drugs is often expected to increase the risk of toxic effects of one or both of the co-administered drugs. Some drugs, such as ketoconazole, present risk of liver damage (including severe cases including liver failure and even requiring liver transplants) and other toxic effects when administered alone; the risk of such toxic effects is believed to be increased when other drugs are concomitantly administered. Where a drug, such as ketoconazole, is known to present a high risk of toxic effects, clinicians will typically avoid its concomitant administration with other drugs.

[0014] However, patients often require treatment with multiple drugs, so that the potential toxicity of drugs such as ketoconazole present disadvantages that can have deleterious consequences for the patient who requires ketoconazole treatment, or may require foregoing the use of ketoconazole or of some other drug which may have otherwise been required for successful treatment.

[0015] Accordingly, improved methods of treatment allowing the administration of other drugs along with CYP3A inhibitors (such as, e.g., ketoconazole) and along with steroidogenesis inhibitors (such as, e.g., ketoconazole) are desired.

SUMMARY

[0016] Applicant discloses herein that CYP3A inhibitors such as, e.g., ketoconazole, may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonist (GRA) mifepristone. Such concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow the reduction in the amount of a GRM, or of a CYP3A inhibitor, administered to the subject; such reduction may

reduce the risk of toxic effects of the CYP3A inhibitor concomitantly administered with the GRM. In embodiments, the CYP3A inhibitor is a strong CYP3A inhibitor. Such concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, may allow the reduction in the amount of GRM administered to the subject, and may allow the reduction in the amount of a CYP3A inhibitor administered to the subject; such reductions may improve treatment of the patient and may reduce the risk of toxic effects of the CYP3A inhibitor.

[0017] Applicant discloses herein that steroidogenesis inhibitors may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonist (GRA) mifepristone. Such concomitant administration of a steroidogenesis inhibitor and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow concomitant administration of a GRA and a steroidogenesis inhibitor, may allow the reduction of the amount of GRM administered to the subject, or may allow the reduction in the amount of a steroidogenesis inhibitor administered to the subject; such reductions may reduce the risk of toxic effects of the steroidogenesis inhibitor. Such concomitant administration of a steroidogenesis inhibitor and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow the reduction in the amount of GRM or of a steroidogenesis inhibitor administered to the subject; such reduction may improve treatment of the subject and may reduce the risk of toxic effects of the steroidogenesis inhibitor.

[0018] For example, Applicant has surprisingly discovered that mifepristone may be administered to patients concomitantly receiving ketoconazole. For example ketoconazole may be administered to patients previously, or concomitantly, also receiving mifepristone so that the patient concomitantly receives ketoconazole and mifepristone. Such concomitant administration of ketoconazole and mifepristone is typically safe for the patient, provides the therapeutic benefits of both drugs to the patient, and may allow the reduction in the amount of mifepristone administered to the subject; such reduction may provide an effective dose of mifepristone that is a lower dose, yet still provides similar plasma mifepristone levels as, and may be as effective as, the dose of mifepristone administered in the absence of ketoconazole. Such concomitant administration of ketoconazole and mifepristone provides the therapeutic benefits of both drugs

to the patient, may allow a reduction in the amount of mifepristone administered to the patient, and may allow the reduction in the amount of ketoconazole administered to the patient; such reduction may reduce the risk of toxic effects of ketoconazole, and may improve the treatment of the patient.

[0019] Applicant's surprising discovery is believed to apply to patients suffering from a disease or disorder and receiving a CYP3A inhibitor, including a strong CYP3A inhibitor such as ketoconazole; such patients suffering from a disease or disorder may be safely administered a GRM, such as mifepristone, concomitantly with the administration of a CYP3A inhibitor such as ketoconazole. Such concomitant administration is believed to be safe for the patient. For example, concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of ketoconazole toxicity in the patient, and is believed to be safe for the patient. In particular, Applicant discloses herein that Cushing's syndrome patients receiving ketoconazole may be safely administered mifepristone concomitantly with the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone to a patient suffering from Cushing's syndrome is believed to be safe for the patient suffering from Cushing's syndrome, which is characterized by hypercortisolism. Patients suffering from Cushing's syndrome, such as those suffering from endogenous Cushing's syndrome, may suffer hyperglycemia secondary to hypercortisolism. Concomitant administration of a GRA (such as, e.g., mifepristone) and a CYP3A inhibitor (such as, e.g., ketoconazole) as disclosed herein is believed to be safe, and to be suitable for controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome.

[0020] In embodiments, a method of treating a patient with Cushing's syndrome, the patient currently taking a GRA at an original dosage, comprises reducing the amount of GRA from said original dosage to an adjusted dosage that is less than the original dosage when the patient is receiving concomitant administration of a CYP3A inhibitor. In embodiments, a method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, the patient currently taking a GRA at an original dosage, comprises reducing the amount of GRA from said original dosage to an adjusted dosage that is less than the original dosage when the patient is receiving concomitant administration of a CYP3A inhibitor. In embodiments of such methods, the adjusted dosage is less than the original dosage by at least an amount selected from about 5%, 10 %, 15 %, 20%, 25 %, 30 %, 33^{1/3} %, 35 %, 40 %, 45%,

50 %, 55 %, 60%, 65 %, $66^{2/3}$ %, 70 %, 75 %, 80%, 85%, and 90% of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least 10 % of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least 25 % of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least $33^{1/3}$ % of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least 50 % of the original dosage.

[0021] In embodiments, where a GRM such as mifepristone would be prescribed at a first GRM dose, the amount of the GRM (such as mifepristone) administered, when co-administered with a steroidogenesis inhibitor or CYP3A inhibitor such as ketoconazole, may be reduced to a reduced GRM dose that has a smaller amount of GRM as compared to the first GRM dose yet provide effective treatment at the reduced GRM dose co-administered with a steroidogenesis inhibitor such as ketoconazole. In embodiments, the clinical status of a subject receiving a reduced GRM dose concomitantly with a steroidogenesis inhibitor may be monitored for clinical response, e.g., for clinical response to the GRM (such as mifepristone). Monitoring for clinical response may include monitoring for clinical effect of the GRM, including clinical efficacy of the GRM; for clinical effect of a steroidogenesis inhibitor or CYP3A inhibitor; for possible adverse reaction to a steroidogenesis inhibitor or CYP3A inhibitor, or the use of a steroidogenesis inhibitor or CYP3A inhibitor in combination with the GRM; for possible side-effects of a steroidogenesis inhibitor or CYP3A inhibitor; for possible side-effects of the use of a steroidogenesis inhibitor or CYP3A inhibitor in combination with the GRM; or combinations thereof.

[0022] In embodiments, the reduced GRM dose may be increased as necessary and as safe for the patient according to such monitoring of the patient. In embodiments, the reduced GRM dose may be titrated upwards as necessary and as safe for the subject according to such monitoring of the patient in order to achieve effective treatment of Cushing's syndrome while remaining safe for the patient with regard to possible adverse effects of the concomitant administration of the GRM and the CYP3A inhibitor, or of the concomitant administration of the GRM and the steroidogenesis inhibitor.

[0023] In embodiments, where a GRM such as mifepristone would be prescribed at a first GRM dose, the amount of the GRM (such as mifepristone) administered, when co-administered with a CYP3A inhibitor, including a strong CYP3A inhibitor such as ketoconazole, may be

reduced to a reduced GRM dose that has a smaller amount of GRM as compared to the first GRM dose yet provide effective treatment at the reduced GRM dose co-administered with a CYP3A inhibitor such as ketoconazole. In embodiments, the clinical status of a patient receiving a reduced GRM dose concomitantly with a CYP3A inhibitor may be monitored, e.g., for clinical effect of the GRM, for clinical effect of the CYP3A inhibitor, for possible adverse reaction to the CYP3A inhibitor or its use in combination with the GRM, for possible side-effects of the CYP3A inhibitor or its use in combination with the GRM, or combinations thereof. In embodiments, the reduced GRM dose may be increased as necessary and as safe for the patient according to such monitoring of the patient. In embodiments, the reduced GRM dose may be titrated upwards as necessary and as safe for the patient according to such monitoring of the patient in order to achieve effective treatment of Cushing's syndrome while remaining safe for the patient with regard to possible adverse effects of the concomitant administration of the GRM and the CYP3A inhibitor.

[0024] Accordingly, Applicant discloses herein that a steroidogenesis inhibitor may be administered to patients concomitantly receiving administration of a GRM. Accordingly, Applicant discloses herein that a CYP3A inhibitor may be administered to patients concomitantly receiving administration of a GRM. For example, Applicant discloses herein that ketoconazole, a steroidogenesis inhibitor and a CYP3A inhibitor, may be administered to patients suffering from a disease or disorder, such as, e.g., Cushing's syndrome, who are concomitantly receiving administration of a GRM such as mifepristone. Such concomitant administration of both a GRA (such as mifepristone) and a CYP3A inhibitor (such as ketoconazole) may be administered to a patient suffering from endogenous Cushing's syndrome to control hyperglycemia secondary to hypercortisolism in the patient.

[0025] Accordingly, Applicant discloses herein that GRMs may be administered to subjects previously, or concomitantly, also receiving administration of a steroidogenesis inhibitor or a CYP3A inhibitor. For example, Applicant discloses herein that GRMs may be administered to subjects suffering from a disease or disorder, such as, e.g., Cushing's syndrome, who previously, or are concomitantly, also receiving administration of a steroidogenesis inhibitor or a CYP3A inhibitor such as ketoconazole. Applicant discloses methods for concomitant administration of a GRM and a steroidogenesis or CYP3A inhibitor such as ketoconazole useful for treating a subject in need of such administration. Subjects in need of such administration

include subjects suffering from a disease or disorder, and include subjects suffering from Cushing's syndrome. Applicant further discloses that such administration of a GRM and a steroidogenesis or a CYP3A inhibitor such as ketoconazole is typically safe for the subject, and provides the therapeutic benefits of both drugs to the subject. In embodiments, such concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRM may allow the reduction in the amount of GRM, or of a steroidogenesis or a CYP3A inhibitor such as ketoconazole, that is administered to the subject; such reductions may reduce the risk of toxic effects of a steroidogenesis or a CYP3A inhibitor such as ketoconazole, such as, e.g., reduce the risk of liver damage to the subject. The GRM may be, e.g., mifepristone.

[0026] Applicant has surprisingly discovered that a steroidogenesis or a CYP3A inhibitor such as ketoconazole may be concomitantly administered with GRMs, such as GRAs, so that concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRA for example may provide safe and effective treatment of a patient in need of treatment. A patient receiving concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRA may be, for example, a patient in need of treatment for Cushing's syndrome (including Cushing's Disease), breast cancer, prostate cancer, ovarian cancer, or other hormone-sensitive cancer. In embodiments, such a patient in need of treatment may receive concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRA, such as mifepristone. In embodiments, such a patient in need of treatment may receive concomitant administration of ketoconazole and mifepristone.

[0027] The methods, compositions, and kits disclosed herein are suitable for use in treating patients suffering from Cushing's syndrome (including Cushing's Disease); or from prostate cancer and other androgen-sensitive cancers; or from breast cancer, ovarian cancer, or other hormone-sensitive cancer (e.g., cancer sensitive to estrogen or progesterone); and are suitable for use in treating subjects suffering from other diseases, disorders, or syndromes.

[0028] In embodiments of the methods disclosed herein, a patient currently receiving a GRM, such as mifepristone, is also concomitantly administered a steroidogenesis or a CYP3A inhibitor such as ketoconazole. In embodiments of the methods disclosed herein, a patient currently receiving a GRM, such as mifepristone, as treatment for a condition characterized by excess steroid levels, or as treatment of a condition that is treated by reducing steroid levels or by reducing steroid effects, is also concomitantly administered a steroidogenesis or a CYP3A

inhibitor such as ketoconazole, whereby the patient is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is cancer, and may be a hormone-sensitive cancer. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

[0029] In embodiments of the methods disclosed herein, a patient currently receiving a steroidogenesis or a CYP3A inhibitor such as ketoconazole is also concomitantly administered a GRM. In embodiments of the methods disclosed herein, a patient currently receiving a steroidogenesis or a CYP3A inhibitor such as ketoconazole as treatment for a condition characterized by excess steroid levels, or as treatment of a condition that is treated by reducing steroid levels or by reducing steroid effects, is also concomitantly administered a GRM, whereby the patient is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is cancer, and may be a hormone-sensitive cancer. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

[0030] Thus, in embodiments of the methods disclosed herein, a patient in need of treatment for a condition is concomitantly administered both a GRM (such as mifepristone) and a steroidogenesis or a CYP3A inhibitor (such as ketoconazole), whereby the patient is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is cancer, and may be a hormone-sensitive cancer. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

[0031] In embodiments, the amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is the same amount, or substantially the same amount, of GRM previously administered to the patient prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, the amount of GRM administered

concomitantly with a steroidogenesis or a CYP3A inhibitor is less than the amount of GRM previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, administration of a reduced amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is an effective amount of GRM; in embodiments, the reduced amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is as effective as the amount of GRM previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. The GRM may be mifepristone. The steroidogenesis or a CYP3A inhibitor may be ketoconazole.

[0032] In embodiments, the amount of steroidogenesis or a CYP3A inhibitor administered concomitantly with the GRM is the same amount, or substantially the same amount, of steroidogenesis or CYP3A inhibitor previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, the amount of steroidogenesis or CYP3A inhibitor administered concomitantly with the GRM is less than the amount of steroidogenesis or CYP3A inhibitor previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, administration of a reduced amount of steroidogenesis or CYP3A inhibitor administered concomitantly with a GRM is an effective amount of steroidogenesis or CYP3A inhibitor; in embodiments, the reduced amount of steroidogenesis or CYP3A inhibitor administered concomitantly with a GRM is as effective as the amount of steroidogenesis or CYP3A inhibitor previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. The GRM may be mifepristone. The steroidogenesis or CYP3A inhibitor may be ketoconazole.

[0033] Concomitant administration of a GRM and steroidogenesis or a CYP3A inhibitor may be administration of a GRM followed within a short time by administration of a steroidogenesis or a CYP3A inhibitor. In embodiments, concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be administration of mifepristone followed within a short time by administration of ketoconazole. Concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be administration of a steroidogenesis or a CYP3A inhibitor followed within a short time by administration of a GRM. In embodiments, concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be

administration of ketoconazole followed within a short time by administration of mifepristone. Concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be simultaneous administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be simultaneous administration of mifepristone and ketoconazole.

[0034] In embodiments, the GRM is a steroidal GRM, such as, e.g., mifepristone. In embodiments, the GRM is a non-steroidal GRM. In embodiments, the GRM is a glucocorticoid receptor antagonist (GRA). In embodiments, the GRA is a steroidal GRA. In embodiments, the GRA is mifepristone. In embodiments, the GRA is a non-steroidal GRA. In embodiments, the GRA is a non-steroidal GRA selected from a GRA having a cyclohexyl-pyrimidine backbone, a GRA having a fused azadecalin backbone, a GRA having a heteroaryl ketone fused azadecalin backbone, and a GRA having an octahydro fused azadecalin backbone.

[0035] In embodiments, a patient is concomitantly administered a GRM and ketoconazole; in embodiments, the GRM is mifepristone. In embodiments, concomitant administration comprises simultaneous administration of a GRM and ketoconazole to a patient, where the GRM is mifepristone. In embodiments, the amount of ketoconazole administered concomitantly with the mifepristone is the same amount, or substantially the same amount, of ketoconazole previously administered to the subject prior to concomitant administration of mifepristone and ketoconazole. In embodiments, the amount of ketoconazole administered concomitantly with the mifepristone is less than the amount of ketoconazole previously administered to the subject prior to concomitant administration of mifepristone and ketoconazole.

[0036] Accordingly, in embodiments, Applicant discloses herein a method for treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome, said patient receiving a first dose of a glucocorticoid receptor antagonist (GRA), said method comprising: concomitantly administering to the patient a dose of a CYP3A inhibitor and a reduced dose of said GRA, wherein said reduced GRA dose consists of a GRA dose that is less than the first GRA dose, whereby the patient is treated for Cushing's syndrome or a condition associated with Cushing's syndrome by concomitant administration of said CYP3A inhibitor and a reduced dose said GRA. Conditions associated with Cushing's syndrome include, without limitation, hyperglycemia secondary to hypercortisolism, e.g., hyperglycemia secondary to

hypercortisolism in a patient suffering from endogenous Cushing's syndrome. Conditions associated with Cushing's syndrome also include, without limitation, hyperglycemia secondary to hypercortisolism in an adult Cushing's syndrome patient who has type 2 diabetes mellitus or glucose intolerance. Conditions associated with Cushing's syndrome further include, without limitation, hyperglycemia secondary to hypercortisolism in an adult Cushing's syndrome patient who has a) type 2 diabetes mellitus or glucose intolerance, and b) has failed surgery or is not a candidate for surgery.

[0037] In embodiments, the dosage of said reduced GRA dose is less than the dosage of said first GRA dose by at least an amount selected from about 5%, 10 %, 15 %, 20%, 25 %, 30 %, 33^{1/3} %, 35 %, 40 %, 45%, 50 %, 55 %, 60%, 65 %, 66^{2/3} %, 70 %, 75 %, 80%, 85%, and 90% of the first GRA dose. In embodiments, the dosage of said reduced GRA dose is less than the dosage of said first GRA dose by about 300 milligrams (mg) of said GRA. In embodiments, the dosage amount of said first GRA dose is 600 mg or higher of said GRA. In embodiments, said reduced GRA dose is a GRA dose selected from the group of GRA doses consisting of about 1500 milligrams (mg) GRA, about 1200 mg GRA, about 900 mg GRA, and about 600 mg GRA. In embodiments, said reduced GRA dose is 900 mg of the GRA. In embodiments, said reduced GRA dose is 600 mg of the GRA. In embodiments, the reduced GRA dose is a daily GRA dose. In embodiments, the methods further comprise titrating upwards the dosage of the reduced GRA dose. In embodiments, such titrating upwards comprises increasing the dosage of the reduced GRA dose in increments of 300 milligrams (mg) of GRA. In embodiments, the interval of time between upward titration of a reduced dose, or of an upwardly titrated reduced dose, and a subsequent upward titration of a dosage of the reduced dose of mifepristone is selected from one week, two weeks, three weeks, and four weeks. In embodiments, the methods include monitoring the patient for clinical response to the GRA. In embodiments, such titrating upwards follows a determination that said reduced GRA dose is associated with a decrease in clinical response to the GRA. In embodiments, monitoring the patient for clinical response to the GRA comprises monitoring the patient for glucose control, anti-diabetic medication requirement, insulin level, psychiatric symptoms, cushingoid appearance, acne, hirsutism, body weight, or combinations thereof. In embodiments, such titrating upwards is capped at a dosage level of 900 milligrams per day. In embodiments, such titrating upwards is capped at a dosage level of 600 milligrams per day. In embodiments of the methods disclosed herein, the reduced GRA dose is a

daily dose of 900 mg mifepristone. In embodiments of the methods disclosed herein, the reduced GRA dose is a daily dose of 600 mg mifepristone.

[0038] Embodiments of the methods disclosed herein are directed to treating a patient suffering from Cushing's syndrome or a condition associated with Cushing's syndrome. In embodiments, the patient suffering from Cushing's syndrome or a condition associated with Cushing's syndrome is a patient suffering from a condition associated with endogenous Cushing's syndrome. In embodiments, treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises treating a patient who is suffering from hyperglycemia secondary to hypercortisolism. In embodiments, treating patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises treating hyperglycemia secondary to hypercortisolism in a Cushing's syndrome patient having type 2 diabetes mellitus or glucose intolerance. In embodiments, treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises treating hyperglycemia secondary to hypercortisolism in a Cushing's syndrome patient, said patient a) having type 2 diabetes mellitus or glucose intolerance, and b) having failed surgery or is not a candidate for surgery. In embodiments, treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises administering mifepristone to control hyperglycemia secondary to hypercortisolism in an adult Cushing's syndrome patient who has a) type 2 diabetes mellitus or glucose intolerance, and b) has failed surgery or is not a candidate for surgery.

[0039] In embodiments, Applicant discloses herein a method for treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome, said patient receiving a first dose of a glucocorticoid receptor antagonist (GRA), said method comprising: concomitantly administering to the patient a dose of said CYP3A inhibitor and a first dose of a glucocorticoid receptor antagonist (GRA), whereby the patient is treated for Cushing's syndrome or a condition associated with Cushing's syndrome by concomitant administration of said CYP3A inhibitor and said GRA. In embodiments, the first GRA dose is selected from a GRA dose no greater than 900 milligrams (mg) per day of the GRA, and no greater than 600 mg per day of the GRA. In embodiments, the patient had been administered a dose of the CYP3A inhibitor prior to said administering of said first GRA dose. In embodiments, said concomitant administration of the CYP3A inhibitor and said GRA comprises administration

of said first GRA dose to a patient having detectable levels of said CYP3A inhibitor, wherein said patient had been administered a dose of the CYP3A inhibitor prior to said administration of said first GRA dose. In embodiments, methods further comprise titrating upwards the dosage of a subsequent GRA dose, wherein the dosage of said subsequent GRA dose is a greater amount of GRA than the amount of GRA of the first GRA dose. In embodiments, such titrating upwards comprises increasing the dosage of the subsequent GRA dose in increments of 300 milligrams (mg) of GRA. In embodiments, the interval of time between upward titration of a subsequent GRA dose, or of an upwardly titrated subsequent GRA dose, and a subsequent upward titration of the dosage of the subsequent GRA dose is selected from one week, two weeks, three weeks, and four weeks.

[0040] In embodiments of the methods disclosed herein, the CYP3A inhibitor is a strong CYP3A inhibitor selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, and voriconazole. In embodiments, the CYP3A inhibitor is ketoconazole.

[0041] In embodiments of the methods disclosed herein, the GRA is mifepristone.

[0042] The methods disclosed herein provide advantages including expanded treatment options for patients suffering from conditions including Cushing's syndrome, Cushing's Disease, prostate cancer, breast cancer, ovarian cancer, and other conditions.

[0043] The methods disclosed herein provide advantages including improved treatments for patients suffering from conditions including Cushing's syndrome, Cushing's Disease, prostate cancer, breast cancer, ovarian cancer, and other conditions, where such improved treatments may include the ability to alter the amount of a GRM, such mifepristone, administered to the patient by administering a GRM such as mifepristone concomitantly with ketoconazole. In embodiments, such improved treatments include the ability to reduce the amount of a GRM, such as mifepristone, administered to a subject.

[0044] The methods disclosed herein provide advantages including improved treatments for patients suffering from conditions including Cushing's syndrome, Cushing's Disease, prostate cancer, breast cancer, ovarian cancer, and other conditions, where such improved treatments may include the ability to alter the amount of ketoconazole administered to the patient by administering a GRM such as mifepristone concomitantly with ketoconazole. In

embodiments, such improved treatments include the ability to reduce the amount of ketoconazole administered to a subject and thus to reduce risk of toxic effects of the ketoconazole.

BRIEF DESCRIPTION of the DRAWINGS

[0045] Fig. 1 shows the mean and standard deviation of mifepristone and its metabolites RU42633, RU42698, and RU42848 measured in healthy male volunteers prior to administration of mifepristone on days one through seventeen. Ketoconazole was also administered on days thirteen – seventeen.

[0046] Fig. 2 shows the plasma concentration profile of mifepristone measured in healthy male volunteers on day twelve (before administration of ketoconazole) and on day seventeen (the fifth day of ketoconazole administration).

DETAILED DESCRIPTION

[0047] Ketoconazole strongly inhibits corticosteroid synthesis; thus, ketoconazole strongly reduces cortisol levels in subjects administered ketoconazole. However, there is concern over its use, for example, due to potential hepatotoxicity (see, e.g., Castinetti et al., *J Clin Endocrinol Metab* 99(5):1623-1630 (2014)).

[0048] According to the U.S. Food and Drug Administration (FDA) definition (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>, accessed February 16, 2017), strong CYP3A inhibitors are expected to increase the AUC of other drugs by greater than five-fold. Ketoconazole is identified by the FDA as a strong CYP3A inhibitor.

[0049] Surprisingly, as disclosed herein, concomitant administration of mifepristone and ketoconazole causes only a small increase in the plasma levels of mifepristone, and does not cause the large increases that would have been expected for such concomitant administration.

[0050] Applicant has surprisingly found that concomitant administration of mifepristone and ketoconazole causes only a small increase in the AUC and in the Cmax of mifepristone in subjects receiving mifepristone alone for twelve days, and then administered both mifepristone and ketoconazole concomitantly. The Cmax of mifepristone administered concomitantly with ketoconazole is increased by less than two-fold (a mere 28% increase in mifepristone Cmax) and the AUC of mifepristone administered concomitantly with ketoconazole is increased by less than two-fold (a mere 38% increase in mifepristone AUC) in subjects receiving 600 mg mifepristone per day who then are given 400 mg ketoconazole (200 mg twice per day)).

[0051] Also surprisingly, as disclosed herein, concomitant administration of ketoconazole and mifepristone also caused smaller increases in ketoconazole levels than would be expected. The Cmax of ketoconazole administered concomitantly with mifepristone is increased by less than four-fold (365% increase in ketoconazole Cmax) and the AUC of ketoconazole administered concomitantly with mifepristone is increased by less than three-fold (253% increase in ketoconazole AUC) when comparing ketoconazole levels on the first day of concomitant administration of both drugs as compared to the ketoconazole levels in subjects on the fifth day of receiving 400 mg ketoconazole (200 mg twice per day) concomitantly with 600 mg mifepristone per day.

[0052] Ketoconazole is a strong inhibitor of steroidogenesis; thus it is believed that ketoconazole may serve as an exemplar for other strong inhibitors of steroidogenesis and that these results indicate that mifepristone, and other glucocorticoid receptor modulators, including other glucocorticoid receptor antagonists, may be safely administered concomitantly with steroidogenesis inhibitors according to the methods disclosed herein.

[0053] Ketoconazole is a strong inhibitor of CYP3A enzymes; thus it is believed that ketoconazole may serve as an exemplar for other strong inhibitors of CYP3A enzymes and that these results indicate that mifepristone, and other glucocorticoid receptor modulators, including other glucocorticoid receptor antagonists, may be safely administered concomitantly with CYP3A enzyme inhibitors according to the methods disclosed herein.

[0054] Applicant discloses herein methods for the safe concomitant administration of both a glucocorticoid receptor modulator (GRM) and steroidogenesis inhibitor to a subject. Applicant discloses herein the surprising finding that both a GRM such as mifepristone and a steroidogenesis inhibitor such as ketoconazole may be safely administered to a subject at the same, or nearly the same, time (i.e., the GRM and the steroidogenesis inhibitor may be concomitantly administered).

[0055] Applicant discloses herein methods for the safe concomitant administration of both a glucocorticoid receptor modulator (GRM) and CYP3A inhibitor to a subject. Applicant discloses herein the surprising finding that both a GRM such as mifepristone and a CYP3A inhibitor such as ketoconazole may be safely administered to a subject at the same, or nearly the same, time (i.e., the GRM and the CYP3A may be concomitantly administered).

[0056] Applicant discloses herein the surprising finding that a subject receiving ketoconazole, which is a steroidogenesis inhibitor and is a CYP3A inhibitor, may also be safely administered an effective dose of mifepristone, which is a glucocorticoid receptor modulator (GRM), e.g., a glucocorticoid receptor antagonist (GRA). Applicant also discloses herein the surprising finding that a subject receiving mifepristone, which is a glucocorticoid receptor modulator (GRM), e.g., a glucocorticoid receptor antagonist (GRA), may also be safely administered ketoconazole, which is a steroidogenesis inhibitor and is a CYP3A inhibitor.

[0057] In embodiments of the methods disclosed herein, a subject receiving a GRM (such as, e.g., a glucocorticoid receptor antagonist (GRA) such as mifepristone) may be safely administered an effective dose of a steroidogenesis inhibitor such as ketoconazole. In embodiments of the methods disclosed herein, a subject may be safely administered ketoconazole and a reduced dose of a GRM, where the reduced dose of a GRM is an effective dose of GRM that is a smaller GRM dose than the GRM dose administered in the absence of a steroidogenesis inhibitor such as ketoconazole. In embodiments of the methods disclosed herein, a subject may be safely administered a GRM and a reduced dose of a steroidogenesis inhibitor such as ketoconazole, where the reduced dose of the steroidogenesis inhibitor is an effective dose of the steroidogenesis inhibitor that is a smaller dose than the a steroidogenesis inhibitor dose administered in the absence of the GRM. In embodiments of the methods disclosed herein, a subject receiving a steroidogenesis inhibitor such as, e.g., ketoconazole, may be safely administered an effective dose of a GRM, such as, e.g., mifepristone. In embodiments of the methods disclosed herein, a subject receiving a GRM, such as, e.g., mifepristone, may be safely administered an effective dose of a steroidogenesis inhibitor such as, e.g., ketoconazole.

[0058] These methods may be applied to subjects suffering from diseases or disorders as well as other subjects, including subjects suffering from Cushing's syndrome. Such concomitant administration of a steroidogenesis inhibitor such as ketoconazole with a GRM would have been expected to produce toxic side effects due to, e.g., an adverse effect on steroidogenesis inhibitor metabolism due to the added GRM (e.g., where the steroidogenesis inhibitor is ketoconazole, a previously safe ketoconazole dose would have been expected to be a toxic dose in the presence of added GRM (e.g., mifepristone)).

[0059] In particular, Applicant discloses herein that patients suffering from a disease or disorder and receiving ketoconazole may be safely administered mifepristone concomitantly with

the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of toxicity in the patient, and is believed to be safe for the patient. In particular, Applicant discloses herein that Cushing's syndrome patients receiving ketoconazole may be safely administered mifepristone concomitantly with the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of toxicity in humans, and is believed to be safe for a patient suffering from Cushing's syndrome.

[0060] Thus, Applicant discloses herein surprising and useful methods for concomitant administration of a steroidogenesis inhibitor such as, e.g., ketoconazole, and a GRM such as, e.g., mifepristone, which provide the benefits of improved treatment without substantially increased risk of adverse treatment side-effects. For example, Applicant provides herein surprising and useful methods for concomitant administration of ketoconazole and mifepristone, which provide the benefits of both drugs without substantially increased risk of ketoconazole toxicity, which can have serious adverse effects on the liver.

[0061] Thus, contrary to the expectation that the presence of a GRM such as mifepristone along with a steroidogenesis inhibitor (e.g., ketoconazole) in a patient would increase the toxicity of the steroidogenesis inhibitor beyond that expected for such a dose of steroidogenesis inhibitor alone, Applicant has discovered that administering a) both a GRM (e.g., mifepristone) and a steroidogenesis inhibitor (e.g., ketoconazole) to a subject, or b) administering a GRM (e.g., mifepristone) to a subject who has recently been given a steroidogenesis inhibitor (e.g., ketoconazole), or c) administering a steroidogenesis inhibitor (e.g., ketoconazole) soon after GRM (e.g., mifepristone) administration to a subject, concomitant administration of a GRM and a steroidogenesis inhibitor does not increase the expected toxicity of the steroidogenesis inhibitor. In embodiments, concomitant administration of a steroidogenesis inhibitor and a GRM allows for administration of an effective dose of GRM that is a reduced GRM dose as compared to the GRM dose administered in the absence of the steroidogenesis inhibitor.

[0062] In embodiments, concomitant administration of ketoconazole and mifepristone allows for administration of an effective dose of mifepristone that is a reduced dose of mifepristone as compared to the mifepristone dose administered in the absence of ketoconazole. For example, Applicant has discovered that concomitant administration of mifepristone and ketoconazole makes it possible to reduce the dose of mifepristone while maintaining sufficient

mifepristone levels for effective therapy for the patient. Such a reduction in mifepristone dose provides the benefit of reducing the amount of mifepristone administered to the subject.

Embodiments in which a subject is concomitantly administered ketoconazole and mifepristone allow for mifepristone dose reduction (as compared to the mifepristone dose in the absence of ketoconazole) include, e.g., Cushing's syndrome and hormone-sensitive cancers such as breast, ovarian, and prostate cancer, and other disorders susceptible of treatment by mifepristone.

[0063] In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is at least about 5% less than the original dose of mifepristone, where the original dose of mifepristone is the dose the subject had been, or would have been, administered in the absence of ketoconazole co-administration. In embodiments, the reduced dose of mifepristone is a dose of mifepristone that is at least about 10% less than the original dose of mifepristone; and may be a dose of mifepristone that is at least about 15%, or about 20%, or about 22%, or about 23%, or about 25%, or about 28%, or about 29%, or about 33%, or about 38%, or about 40%, or about 50%, or about 66%, or about 75% less than the original dose of mifepristone.

[0064] In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is 300 mg less mifepristone than the amount of the original dose of mifepristone. In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is an amount of mifepristone that is an integer multiple of 300 mg mifepristone less than the amount of the original dose of mifepristone. In embodiments, the integer of the integer multiple is selected from the integers 1, 2, 3, 4, and 5.

[0065] In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is about 900 mg mifepristone; or is about 600 mg mifepristone; or is about 300 mg mifepristone. In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is about 300 mg mifepristone administered only every other day; or is about 300 mg mifepristone administered every third day; or is about 300 mg mifepristone administered every fourth day. For example, where the original dose of mifepristone is about 1500 mg per day, the reduced dose of mifepristone may be about 1200 mg of mifepristone administered every day; or may be about 900 mg of mifepristone administered

every day; or may be about 600 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every day. For example, where the original dose of mifepristone is about 1200 mg per day, the reduced dose of mifepristone may be about 900 mg of mifepristone administered every day; or may be about 600 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every day. For example, where the original dose of mifepristone is about 900 mg per day, the reduced dose of mifepristone may be about 600 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every other day. For example, where the original dose of mifepristone is about 600 mg per day, the reduced dose of mifepristone may be about 300 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every other day; or may be about 300 mg of mifepristone administered every third day. For example, where the original dose of mifepristone is about 300 mg per day, the reduced dose of mifepristone may be about 300 mg of mifepristone administered every other day; or may be about 300 mg of mifepristone administered every third day; or may be about 300 mg of mifepristone administered every fourth day.

[0066] In embodiments in which a subject has been receiving about 1800 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 1500 mg mifepristone per day; may be about 1200 mg mifepristone per day; may be about 900 mg mifepristone per day; may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 1500 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 1200 mg mifepristone per day; may be about 900 mg mifepristone per day; may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 1200 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 900 mg mifepristone per day; may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg

mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 900 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 600 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; may be about 300 mg every third day; or may be about 300 mg mifepristone every fourth day. In embodiments in which a subject has been receiving about 300 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 300 mg mifepristone every other day; may be about 300 mg every third day; or may be about 300 mg mifepristone every fourth day.

[0067] In embodiments in which a subject has been receiving a first dose of mifepristone (e.g. a daily dose of mifepristone of about 1800 mg/day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day), and concomitant administration of mifepristone and ketoconazole is indicated, the subject may be administered a reduced dose of mifepristone, where the amount of the reduced dose is less than the original mifepristone dose by about 300 mg mifepristone per day, and the subject may be monitored for clinical effects of the drugs, including monitoring for clinical response to mifepristone. In embodiments in which a subject has been receiving a first dose of mifepristone (e.g. a daily dose of mifepristone of about 1800 mg/day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day), and concomitant administration of mifepristone and ketoconazole is indicated, the subject may be administered a reduced dose of mifepristone, where the amount of the reduced dose is less than the original mifepristone dose by about 300 mg mifepristone per day, and the reduced dose of mifepristone may be subsequently titrated upwards (i.e., increased in subsequent dose administrations) in increments of about 300 mg mifepristone. In embodiments, such upward titration of the reduced dose in increments of 300 mg/day may be subjected to a maximum daily dosage of about 600 mg/day, or of about 900 mg/day, or of about 1200 mg/day, or of about 1500 mg/day. In embodiments, such upward

titration of the dosage of the reduced daily dose of mifepristone administered per day is capped at a maximum daily dose, wherein said maximum daily dose is selected from the group consisting of 900 milligrams (mg) mifepristone per day and 600 mg mifepristone per day.

[0068] The subject may be monitored for clinical effects of the drugs, e.g., for clinical response to the GRA (e.g., mifepristone), adverse events, side-effects of any drug, at any stage or at all stages, of such incremental upward titration of the mifepristone dosage. The interval of time between administration of a reduced dose, or of an upwardly titrated reduced dose, and an upward titration of a dose of mifepristone may be an interval selected from two days, four days, one week, two weeks, one month, two months, and three months. In embodiments, the interval of time between upward titration of a reduced dose, or of an upwardly titrated reduced dose, and a subsequent upward titration of a dosage of the reduced dose of mifepristone is selected from one week, two weeks, three weeks, and four weeks. Monitoring the patient for clinical response may include monitoring the patient (e.g., to identify or determine if there are changes in) for glucose control, anti-diabetic medication requirement, insulin level, psychiatric symptoms, cushingoid appearance, acne, hirsutism, and monitoring the body weight of the patient (e.g., to identify or determine if there are changes in any one or more of these symptoms and characteristics).

[0069] In embodiments in which a subject has been receiving a first dose of mifepristone (e.g. a daily dose of mifepristone of about 1800 mg/day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day), and concomitant administration of mifepristone and ketoconazole is indicated, the subject may be administered a reduced dose of mifepristone, where the amount of the reduced dose is less than the original mifepristone dose, and the reduced dose of mifepristone may be about 1500 mg mifepristone per day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day; and the subject may be monitored for clinical response to the GRA, or for other clinical effects of the drugs. In such embodiments, the reduced dose of mifepristone may be subsequently titrated upwards (i.e., increased in subsequent dose administrations) in increments of about 300 mg mifepristone. In embodiments, such upward titration of the reduced dose in increments of 300 mg/day may be subjected to a maximum daily dosage of about 600 mg/day, or of about 900 mg/day, or of about 1200 mg/day, or of about 1500 mg/day. In embodiments, such upward titration of the dosage of the reduced daily dose of mifepristone administered per day is capped at a maximum daily dose, wherein said maximum daily dose is

selected from the group consisting of 900 milligrams (mg) mifepristone per day and 600 mg mifepristone per day.

[0070] The subject may be monitored for clinical response to the drugs, including e.g., clinical response to the GRA (e.g., mifepristone), for adverse events, side-effects of any of the drugs, at any stage, or at all stages, of such incremental upward titration of the mifepristone dosage. Upward titration of a reduced dose of mifepristone may be performed every two days, or every four days, or every week, or every two weeks, or every month, or every two months. In embodiments, the interval of time between upward titration of a reduced dose, or of an upwardly titrated reduced dose, and a subsequent upward titration of a dosage of the reduced dose of mifepristone is selected from one week, two weeks, three weeks, and four weeks.

[0071] Applicant discloses herein that concomitant treatment with both mifepristone and ketoconazole may lead to small increases in plasma levels of mifepristone as measured by C_{max} and as measured by AUC. For example, as disclosed in Table 3 below, concomitant administration of mifepristone and ketoconazole led to about 28% (27.59%, or about 30%) increase in mifepristone C_{max} and about 38% (38.01%, about 40%) increase in mifepristone AUC. Thus, in embodiments, a mifepristone dose administered to a subject receiving concomitant administration of mifepristone and ketoconazole may be reduced in compensation for such a small increase in mifepristone plasma levels. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 22% of the original dose of mifepristone. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 23% of the original dose of mifepristone. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 28% of the original dose of mifepristone. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 29% of the original dose of mifepristone. In embodiments, the reduced dose of mifepristone is a dose of mifepristone that is at least about 90% of the original dose of mifepristone; and may be a dose of mifepristone that is at least about 85%, or about 80%, or about 78%, or about 77%, or about 75%, or about 72%, or

about 71%, or about 67%, or about 62%, or about 60%, or about 50%, or about 34%, or about 25% of the original dose of mifepristone.

[0072] Applicant further discloses herein that, since mifepristone provides added therapeutic benefit synergistic with that of ketoconazole, concomitant administration of mifepristone and ketoconazole makes it possible to reduce the dose of ketoconazole while maintaining mifepristone levels effective for therapy for a patient. Such a reduction in ketoconazole dose provides the benefit of reducing the risk of toxic side-effects associated with all ketoconazole treatments. Thus, concomitant administration of ketoconazole and mifepristone, by allowing reduced ketoconazole dose, provides improved, synergistic therapeutic benefits. In embodiments, such ketoconazole dose reduction may be used to wean the patient off ketoconazole, leading to lower and lower ketoconazole doses, thereby reducing the risk of ketoconazole toxicity. In embodiments, such ketoconazole dose reduction may be used to wean the patient off ketoconazole, leading to lower and lower ketoconazole doses, with concomitant upward adjustment of mifepristone dosage as needed, ultimately leading to treatment with mifepristone alone and cessation of ketoconazole treatment (lessening the risk of liver damage and other toxicities). Embodiments in which concomitant administration of ketoconazole and mifepristone may lead to ketoconazole dose reduction (as compared to the ketoconazole dose in the absence of mifepristone) include, e.g., Cushing's syndrome and hormone-sensitive cancers such as breast, ovarian, and prostate cancer, and other disorders susceptible of treatment by mifepristone.

[0073] In embodiments, concomitant administration of ketoconazole and mifepristone allows for administration of an effective dose of ketoconazole that is a reduced dose of ketoconazole as compared to the ketoconazole dose administered in the absence of mifepristone. For example, Applicant discloses herein that concomitant administration of mifepristone and ketoconazole makes it possible to reduce the dose of ketoconazole while maintaining effective therapy for the patient. Such a reduction in ketoconazole dose provides the benefit of reducing the amount of ketoconazole administered to the subject. Embodiments in which a subject is concomitantly administered ketoconazole and mifepristone allow for ketoconazole dose reduction (as compared to the ketoconazole dose in the absence of mifepristone) include, e.g., Cushing's syndrome and hormone-sensitive cancers such as breast, ovarian, and prostate cancer, and other disorders susceptible of treatment by ketoconazole and other steroidogenesis inhibitors.

[0074] In embodiments, the reduced dose of ketoconazole administered to a subject also concomitantly receiving mifepristone is a dose of ketoconazole that is at least about 5% less than the original dose of ketoconazole, where the original dose of ketoconazole is the dose the subject had been, or would have been, administered in the absence of mifepristone co-administration. In embodiments, the reduced dose of ketoconazole is a dose of ketoconazole that is at least about 10% less than the original dose of ketoconazole; and may be a dose of ketoconazole that is at least about 15%, or about 20%, or about 25%, or about 33%, or about 50%, or about 66%, or about 75% less than the original dose of ketoconazole.

[0075] Applicant provides definitions of some terms used in the present disclosure.

[0076] DEFINITIONS

[0077] The abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0078] “Patient”, “patient in need”, “subject”, “subject in need” and the like refer to a person having, or suspected of having, a disease or condition which may be treated by administration of a therapeutic drug.

[0079] As used herein, the term “Cushing’s syndrome” refers to an array of symptoms caused by excess cortisol. Cushing’s syndrome includes endogenous Cushing’s syndrome and ectopic Cushing’s syndrome. Such symptoms include, for example, elevated blood pressure, elevated blood glucose, increased weight (typically in the mid-section, and in the face causing a characteristic “moon-face”), immune suppression, thin skin, acne, depression, hirsutism, and other symptoms.

[0080] As used herein, “Cushing’s Disease” refers to pituitary-dependent Cushing’s syndrome, e.g., excess cortisol caused by pituitary abnormality (typically a pituitary tumor). Cushing’s Disease is thus a disease that is a particular type of Cushing’s syndrome. The term Cushing’s syndrome thus includes reference to Cushing’s Disease.

[0081] As used herein, a “patient suffering from Cushing’s syndrome” refers to any patient suffering from Cushing’s syndrome, including endogenous Cushing’s syndrome; Cushing’s Disease; or a condition associated with Cushing’s syndrome. A condition associated with Cushing’s syndrome may be, without limitation, a condition associated with endogenous Cushing’s syndrome; hyperglycemia secondary to hypercortisolism; a condition of hypercortisolism in an endogenous Cushing’s syndrome patient, said patient having type 2

diabetes mellitus or glucose intolerance; a condition of hyperglycemia secondary to hypercortisolism in an endogenous Cushing's syndrome patient, said patient having type 2 diabetes mellitus or glucose intolerance and having failed surgery; hyperglycemia secondary to hypercortisolism in an endogenous Cushing's syndrome patient, said patient having type 2 diabetes mellitus or glucose intolerance and having failed surgery or who is not a candidate for surgery; and other conditions associated with Cushing's syndrome.

[0082] "Treat", "treating" and "treatment" refer to any indicia of success in the treatment or amelioration of a pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination; histopathological examination (*e.g.*, analysis of biopsied tissue); laboratory analysis of urine, saliva, tissue samples, serum, plasma, or blood; or imaging.

[0083] As used herein, "treating a patient who is suffering from Cushing's syndrome", or treating a subject who is suffering from Cushing's syndrome", or similar phrases refer to, without limitation, treating a patient suffering from Cushing's syndrome, including endogenous Cushing's syndrome; treating a patient suffering from Cushing's Disease; or treating a patient suffering from a condition associated with Cushing's syndrome. A condition associated with Cushing's syndrome is discussed above. For example, treating a patient who is suffering from Cushing's syndrome may include administering mifepristone or other GRA to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

[0084] As used herein, the term "administration" refers to the delivery of a drug or other therapeutic into the body of a patient in need of treatment by the drug or therapeutic, effective to achieve a therapeutic effect. Administration may be by any suitable route of administration, including, for example, oral administration; intravenous administration; subcutaneous administration; parenteral administration; intra-arterial administration; nasal administration; topical administration; and other routes of administration.

[0085] As used herein, the terms “per cent”, “%” and “weight percent” when applied to a dosage administered to a subject, all refer to a percentage taken by comparing the weight of a first dose to that of a second dose, and multiplying the resulting decimal fraction by 100. Thus, for example, where an original mifepristone dose is 1200 milligrams (mg), a dose that is reduced by 50% is a dose of 600 mg mifepristone; and where an original mifepristone dose is 600 milligrams (mg), a dose that is reduced by 50% is a dose of 300 mg mifepristone; and so forth.

[0086] As used herein, the phrases “less than x by at least”, “less than x by at least about”, and the like refer to amounts equal to and less than the x , where x is a number. For example, the phrase “less than the original dosage by at least 25%” refers to dosage amounts that include 25% less than the original dosage as well as other percentages (e.g., 26%, 28%, etc.) less than the original dosage amount.

[0087] As used herein, the terms “effective amount,” “amounts effective,” therapeutic amount”, and “therapeutically effective amount” refer to an amount or amounts of one or more pharmacological agents effective to treat, eliminate, or mitigate at least one symptom of the disease being treated. In some cases, “effective amount,” “amounts effective,” “therapeutic amount”, and “therapeutically effective amount” can refer to an amount of a functional agent or of a pharmaceutical composition useful for exhibiting a detectable therapeutic or inhibitory effect.

[0088] As used herein, the term “simultaneously or sequentially administering” refers to administration of two compounds, such as a GRA and a CYP3A inhibitor, such that the two compounds are in the body at the same time in therapeutically effective amounts.

[0089] As used herein, “concomitant” means at the same, or nearly the same, time, and “concomitantly” refers to actions performed at the same, or nearly the same, time. As used herein, the terms “concurrent” and “concomitant” are equivalent and may be used interchangeably. The adverbs “concurrently” and “concomitantly” are equivalent and may be used interchangeably.

[0090] As used herein, the term “concomitant administration” of two or more drugs means administering two or more drugs at the same, or nearly the same, time. Concomitant administration of two or more drugs provides therapeutically effective amounts of the two or more drugs in the system of the subject at the same time. Concomitant administration includes administration of a GRA to a patient who has previously been administered a drug, such as a

CYP3A inhibitor or a steroidogenesis inhibitor, and therapeutically effective levels of the CYP3A inhibitor or steroidogenesis inhibitor remain in the patient when the patient is administered the GRA (e.g., when the patient is administered mifepristone), and includes administration of a CYP3A inhibitor or a steroidogenesis inhibitor to a patient who has previously been administered a drug, such as a GRA, and therapeutically effective levels of the GRA remain in the patient when the patient is administered the CYP3A inhibitor or steroidogenesis inhibitor.

[0091] As used herein, “concomitantly administering drugs” means that two or more drugs are administered to a subject at the same, or nearly the same, time. Drugs that are concomitantly administered will each be present in therapeutically effective amounts in the system of the subject at the same time. Nearly the same time means that only a short amount of time separates two events, such as administration of a first drug and the administration of a second drug.

[0092] Events or actions that are “simultaneous” or that occur or are performed “simultaneously” are events that occur or are performed at the same time.

[0093] As used herein, “at the same time” means that two events occur or are performed within about five minutes of each other.

[0094] As used herein, “nearly the same time” means that two events occur or are performed within about a short time of each other.

[0095] As used herein, a “short time”, a “short amount of time”, a “short period of time”, and the like mean a time that is less than about two hours, or less than about one hour, or less than about 45 minutes, or less than about 30 minutes, or less than about 20 minutes, or less than about 10 minutes, or less than about 7 minutes.

[0096] As used herein, the term “clinical effect” means changes in symptoms or signs characteristic of, or indicative of, a clinical condition or disorder. For example, where a subject is treated for Cushing’s syndrome, including Cushing’s Disease, a clinical effect may be a change in any one or more of blood pressure, blood glucose, other pre-diabetic symptom, weight, mid-section perimeter, facial characteristics (e.g., change in “moon-face” appearance), immune function, skin thickness, acne, depression or other mood symptom, hirsutism, and other symptoms.

[0097] As used herein, “monitoring for clinical response”, e.g., monitoring a patient for clinical response to a GRA such as mifepristone, may include monitoring the patient (e.g., to identify or determine if there are changes in) for glucose control, anti-diabetic medication requirement, insulin level, psychiatric symptoms, cushingoid appearance, acne, hirsutism, and monitoring the body weight of the patient (e.g., to identify or determine if there are changes in any one or more of these symptoms and characteristics). Monitoring for clinical response may also include monitoring a patient for adverse events, for side-effects of any drug (including a GRA, a CYP3A inhibitor, a steroidogenesis inhibitor, and combinations of these). Thus, monitoring for clinical response may include monitoring for clinical effect of a drug such as a GRM, including clinical efficacy of the GRM; for clinical effect of a steroidogenesis inhibitor or CYP3A inhibitor; for possible adverse reaction to a steroidogenesis inhibitor or CYP3A inhibitor; for possible adverse reaction to the use of a steroidogenesis inhibitor or CYP3A inhibitor in combination with the GRM; for possible side-effects of a steroidogenesis inhibitor or CYP3A inhibitor, or their use in combination with the GRM; or combinations thereof.

[0098] As used herein, the term “AUC” means the area under the plasma concentration-time curve, and serves as a measure of the plasma levels of a drug in a subject to whom the drug has been administered.

[0099] As used herein, the term “C_{max}” means the maximum observed plasma concentration of a drug in a subject to whom the drug has been administered.

[00100] As used herein, the term “binding” refers to persistent contact, or adherence (however brief or intermittent), between two compounds.

[00101] As used herein, the terms “affinity”, “binding affinity”, and related terms refer to the strength and specificity of binding, such as binding between a ligand and its receptor. “Higher affinity” is used with reference to comparative binding between two ligands to a receptor, where the ligand which binds with higher affinity binds at a lower concentration than does the “lower affinity” ligand. For example, in a competitive binding experiment, a high affinity ligand will compete with a reference ligand for binding to a receptor at a lower concentration than will the low affinity ligand compete for binding at the receptor.

[00102] The term “specific binding” refers to binding that is more selective, and typically stronger, than mere non-specific adhesion between compounds. Specific binding may be exemplified by the binding which occurs between a ligand and its receptor.

[00103] Description of compounds useful in the methods disclosed herein, and suitable for the pharmaceutical compositions disclosed herein are described in accordance with principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, or physiological conditions.

[00104] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[00105] "Alkyl" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C_{1-2} , C_{1-3} , C_{1-4} , C_{1-5} , C_{1-6} , C_{1-7} , C_{1-8} , C_{1-9} , C_{1-10} , C_{2-3} , C_{2-4} , C_{2-5} , C_{2-6} , C_{3-4} , C_{3-5} , C_{3-6} , C_{4-5} , C_{4-6} and C_{5-6} . For example, C_{1-6} alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec.*butyl, *tert.*butyl, pentyl, isopentyl, hexyl, *etc.*

[00106] "Alkoxy" refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O-. As for the alkyl group, alkoxy groups can have any suitable number of carbon atoms, such as C_{1-6} . Alkoxy groups include, for example, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, 2-butoxy, *iso*-butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, hexoxy, *etc.*

[00107] "Halogen" refers to fluorine, chlorine, bromine and iodine.

[00108] "Haloalkyl" refers to alkyl, as defined above, where some or all of the hydrogen atoms are replaced with halogen atoms. As for the alkyl group, haloalkyl groups can have any suitable number of carbon atoms, such as C_{1-6} . For example, haloalkyl includes trifluoromethyl, fluoromethyl, *etc.* In some instances, the term "perfluoro" can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For example, perfluoromethane includes 1,1,1-trifluoromethyl.

[00109] "Haloalkoxy" refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for the alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as C_{1-6} . The alkoxy groups can be substituted with 1, 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by

fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, *etc.*

[00110] “Cycloalkyl” refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈, C₃₋₉, C₃₋₁₀, C₃₋₁₁, and C₃₋₁₂. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring. Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. When cycloalkyl is a saturated monocyclic C₃₋₈ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. When cycloalkyl is a saturated monocyclic C₃₋₆ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00111] “Heterocycloalkyl” refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and -S(O)₂-. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxalidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline.

[00112] When heterocycloalkyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocycloalkyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

[00113] "Aryl" refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can include any suitable number of ring atoms, such as, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, as well as from 6 to 10, 6 to 12, or 6 to 14 ring members. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted.

[00114] "Heteroaryl" refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can also be oxidized, such as, but not limited to, N-oxide, -S(O)- and -S(O)₂-. Heteroaryl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl

ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

[00115] The heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6- pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and 5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes 2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

[00116] Some heteroaryl groups include those having from 5 to 10 ring members and from 1 to 3 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring heteroatoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.

[00117] Some heteroaryl groups include from 5 to 10 ring members and only nitrogen heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, and cinnoline. Other heteroaryl groups include from 5 to 10 ring members and only oxygen heteroatoms, such as furan and benzofuran. Some other heteroaryl groups include from 5 to 10 ring members and only sulfur heteroatoms, such as thiophene and benzothiophene. Still other heteroaryl groups include from 5 to 10 ring members and at least two heteroatoms, such as imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiazole, isothiazole, oxazole, isoxazole, quinoxaline, quinazoline, phthalazine, and cinnoline.

[00118] "Heteroatoms" refers to O, S or N.

[00119] "Salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

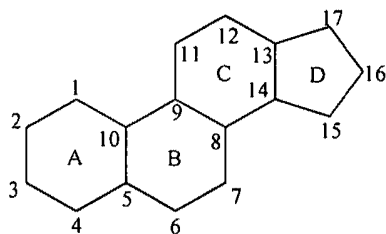
[00120] "Isomers" refers to compounds with the same chemical formula but which are structurally distinguishable.

[00121] "Tautomer" refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one form to another.

[00122] As used herein, the term "ketoconazole" refers to the molecule having the chemical name "1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine"; it is sold for clinical use under the name "Nizoral[®]", and may also be referred to by the abbreviation "keto".

[00123] As used herein, the terms "steroid" and "steroids", and the phrase "steroidal backbone" in the context of glucocorticoid receptor antagonists containing such refers to glucocorticoid receptor antagonists that contain modifications of the basic structure of cortisol,

an endogenous steroidal glucocorticoid receptor ligand. The basic structure of a steroidal backbone is provided as Formula I:

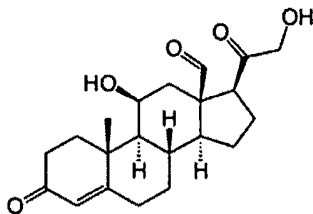


Formula I: Steroidal Backbone

The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11- β hydroxy group and modification of the 17- β side chain (*See, e. g., Lefebvre (1989) J. Steroid Biochem. 33: 557-563*).

[00124] As used herein, the terms “progesterone receptor” and “PR” refer to a naturally occurring receptor which binds progesterone.

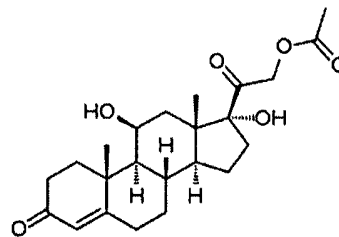
[00125] The term “aldosterone” refers to the naturally occurring mineralocorticoid



hormone having the structure:

[00126] A mineralocorticoid receptor (MR), also known as a type I glucocorticoid receptor (GR I), is activated by aldosterone in humans.

[00127] The term "cortisol" refers to the naturally occurring glucocorticoid hormone (also



known as hydrocortisone) having the structure:

[00128] As used herein, the term glucocorticoid receptor (GR) refers to a receptor that binds a glucocorticoid, such as cortisol, dexamethasone, or other molecules. A glucocorticoid receptor, also known as a corticosteroid receptor or as a type II glucocorticoid receptor (GR II),

and in humans, as a cortisol receptor, is activated by cortisol in humans (or, e.g., by corticosterone (“cortisone”) in some other animals, such as rats and mice). The human cortisol receptor (GR II receptor, Genbank: P04150) specifically binds to cortisol and/or cortisol analogs (e.g. dexamethasone). The term includes isoforms of GR II, recombinant GRII, and mutated GRII.

[00129] As used herein, the term glucocorticoid receptor modulator (GRM) refers to an agent that affects the action of a glucocorticoid receptor (GR). Such modulation may include activation (agonist action), partial activation (partial agonist action), inhibition (reduction in activation of the receptor under conditions where it would otherwise be activated, such as in the presence of cortisol), and blockade (complete or near complete suppression of activation of the receptor under conditions where it would otherwise be activated, such as in the presence of cortisol). GRMs may affect the activity of a GR by increasing or by decreasing the activity of the GR. GRMs include steroids, and, in embodiments, include pyrimidinediones; azadecalins; fused-ring azadecalins; heteroaryl-ketone fused-ring azadecalins; and other compounds.

[00130] As used herein, the terms “glucocorticoid agonist”, “glucocorticoid receptor agonist”, “glucocorticoid receptor type II agonist”, and “GRII agonist” refer to a compound or agent which may bind to and activate a cortisol receptor. Such agents include, for example, cortisol, dexamethosone, prednisone, and other compounds and agents which bind to and activate a GRII.

[00131] As used herein, the terms “glucocorticoid antagonist”, “glucocorticoid receptor antagonist”, “glucocorticoid antagonist”, “glucocorticoid receptor type II antagonist”, “GRII antagonist”, and “GRA” refer to agents that inhibit the action of a cortisol receptor; such inhibition may include interfering with the binding of a glucocorticoid agonist such as cortisol, dexamethosone, or other compound or agent which may bind to and activate a cortisol receptor. A GRA is a glucocorticoid receptor modulator. Inhibition constants (K_i) for GRAs against the human cortisol receptor may be between about 0.0001 nM and about 1,000 nM; preferably may be between about 0.0005 nM and about 10 nM, and most preferably between about 0.001 nM and about 1nM.

[00132] The term "glucocorticoid receptor antagonist" refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to

a GR. A "specific glucocorticoid receptor antagonist" refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. By "specific," we intend the drug to preferentially bind to the GR rather than another nuclear receptors, such as mineralocorticoid receptor (MR) or progesterone receptor (PR).

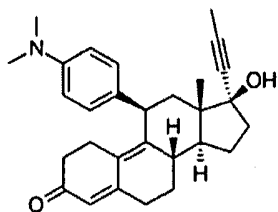
[00133] By "specific," the drug preferentially binds to the GR rather than other nuclear receptors, such as mineralocorticoid receptor (MR), androgen receptor (AR), or progesterone receptor (PR). It is preferred that the specific glucocorticoid receptor antagonist bind GR with an affinity that is 10x greater ($1/10^{\text{th}}$ the K_d value) than its affinity to the MR, AR, or PR. In a more preferred embodiment, the specific glucocorticoid receptor antagonist binds GR with an affinity that is 100x greater ($1/100^{\text{th}}$ the K_d value) than its affinity to the MR, AR, or PR.

[00134] In embodiments, a glucocorticoid receptor modulator (GRM) is a glucocorticoid receptor antagonist (GRA). In embodiments, the GRA is an antagonist of a glucocorticoid type II (GRII) receptor. In embodiments, the GRA binds preferentially to a GRII receptor as compared to its binding to a glucocorticoid type I (GRI) receptor. In embodiments, the GRA reduces the activation of a GRII receptor. In embodiments, the GRA reduces the activity of a GRII receptor. In embodiments, the GRA may bind to a progesterone receptor (PR), and may bind to a glucocorticoid receptor with higher affinity than it binds to PR. In embodiments, the GRA is mifepristone. In embodiments, the GRA is a selective inhibitor of the glucocorticoid receptor. In embodiments, the GRA may only poorly bind to PR, or may not measurably bind to PR.

[00135] As used herein, a "steroidal glucocorticoid receptor antagonist" means a molecule including a steroid backbone structure which antagonizes the binding of cortisol, corticosterone, or dexamethasone to a glucocorticoid receptor, or which reduces or blocks the activation of a glucocorticoid receptor by cortisol, corticosterone, or dexamethasone. Examples of steroidal glucocorticoid receptor antagonists include mifepristone, monodemethylated mifepristone, didemethylated mifepristone, 17- α -[3'-hydroxy-propynyl]mifepristone, ulipristal (CDB-2914), CDB-3877, CDB-3963, CDB-3236, CDB-4183, cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11-(4-dimethylaminoethoxyphenyl)-17-(propynyl)-17-(hydroxy-4,9-estradien-3-one, and 17-(hydroxy-17-(19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

[00136] Mifepristone is a GRA, which binds to GRII (and which also binds to a progesterone receptor). As used herein, the term "mifepristone" refers to 11 β -(4-

dimethylaminophenyl)-17 β -hydroxy-17 α -(1-propynyl)-estra-4,9-dien-3-one), also referred to as RU486, or as RU38.486, or as 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one). Mifepristone binds to the glucocorticoid receptor (GR), typically with high affinity, and inhibits the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Salts, hydrates and prodrugs of mifepristone are all included in the term “mifepristone” as used herein. Thus, used herein, “mifepristone” refers to the molecule that has the following structure:



and to salts, hydrates and prodrugs thereof, and pharmaceutical compositions thereof.

Mifepristone is also sometimes abbreviated as “mife” and “MIFE”.

[00137] Metabolites of mifepristone include RU42633 (desmethylmifepristone: (8S,11R,13S,14S,17S)-17-hydroxy-13-methyl-11-[4-(methylamino)phenyl]-17-prop-1-ynyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one); RU42698 (22-hydroxy mifepristone: (8S,11R,13S,14S,17S)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(3-hydroxyprop-1-ynyl)-13-methyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one); and RU42848 (didesmethylmifepristone: (8S,11R,13S,14S,17S)-11-(4-aminophenyl)-17-hydroxy-13-methyl-17-prop-1-ynyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one), among others.

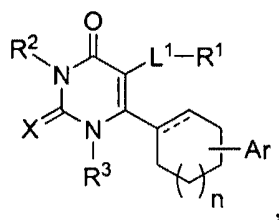
[00138] In some embodiments, the GRA comprises a steroidal backbone with at least one phenyl-containing moiety in the 11- β position of the steroidal backbone. In some cases, the phenyl-containing moiety in the 11- β position of the steroidal backbone is a dimethylaminophenyl moiety. In some cases, the GRA is mifepristone. In some embodiments, the GRA is selected from the group consisting of 11 β -(4-dimethylaminoethoxyphenyl)-17 α -propynyl-17 β -hydroxy-4,9 estradien-3-one and (17 α)-17-hydroxy-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one. In some embodiments, the GRA is (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

[00139] As used herein, the phrase “non-steroidal backbone” in the context of glucocorticoid receptor antagonists containing such refers to glucocorticoid receptor antagonists

that do not share structural homology to, or are not modifications of, cortisol. Such compounds include, for example, small molecules, synthetic mimetics and analogs of proteins, including partially peptidic, pseudopeptidic and non-peptidic molecular entities.

[00140] In some embodiments, the GRA is a non-steroidal compound. In embodiments, non-steroidal GRA compounds include compounds having a cyclohexyl-pyrimidine backbone; non-steroidal GRA compounds having a fused azadecalin backbone; non-steroidal GRA compounds having a heteroaryl ketone fused azadecalin backbone; and non-steroidal GRA compounds having an octahydro fused azadecalin backbone. Exemplary glucocorticoid receptor antagonists having a cyclohexyl-pyrimidine backbone include those described in U.S. Patent No. 8,685,973. Exemplary glucocorticoid receptor antagonists having a fused azadecalin backbone include those described in U.S. Patent Nos. 7,928,237; and 8,461,172. Exemplary glucocorticoid receptor antagonists having a heteroaryl ketone fused azadecalin backbone include those described in U.S. Patent No. 8,859,774. Exemplary glucocorticoid receptor antagonists having an octahydro fused azadecalin backbone include those described in U.S. Patent Application Publication 20150148341.

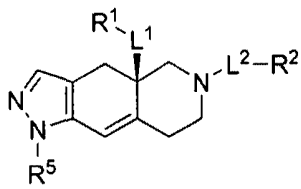
[00141] In some cases, the GRA having a non-steroidal backbone is a cyclohexyl pyrimidine. In some cases, wherein the cyclohexyl pyrimidine has the following formula:



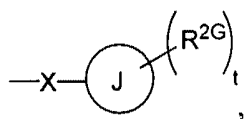
[00142] wherein the dashed line is absent or a bond; X is selected from the group consisting of O and S; R¹ is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, optionally substituted with from 1 to 3 R^{1a} groups; each R^{1a} is independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkyl OR^{1b}, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, OR^{1b}, NR^{1b}R^{1c}, C(O)R^{1b}, C(O)OR^{1b}, OC(O)R^{1b}, C(O)NR^{1b}R^{1c}, NR^{1b}C(O)R^{1c}, SO₂R^{1b}, SO₂NR^{1b}R^{1c}, cycloalkyl, heterocycloalkyl, aryl and heteroaryl; R^{1b} and R^{1c} are each independently selected from the group consisting of H and C₁₋₆ alkyl; R² is selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ alkyl-OR^{1b}, C₁₋₆ alkyl NR^{1b}R^{1c} and C₁₋₆ alkylene heterocycloalkyl; R³ is selected from the group consisting of H and C₁₋₆ alkyl; Ar is aryl, optionally substituted with 1-4 R⁴ groups; each R⁴ is independently selected

from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy; L¹ is a bond or C₁₋₆ alkylene; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

[00143] In some cases, the GRA having a non-steroidal backbone is a fused azadecalin. In some cases, the fused azadecalin is a compound having the following formula:

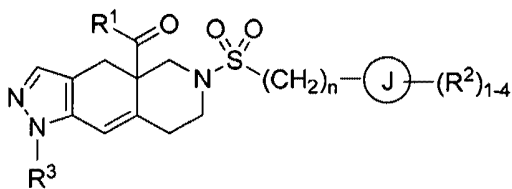


wherein L¹ and L² are members independently selected from a bond and unsubstituted alkylene; R¹ is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, -OR^{1A}, NR^{1C}R^{1D}, -C(O)NR^{1C}R^{1D}, and -C(O)OR^{1A}, wherein R^{1A} is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl, R^{1C} and R^{1D} are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl, wherein R^{1C} and R^{1D} are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen; R² has the formula:



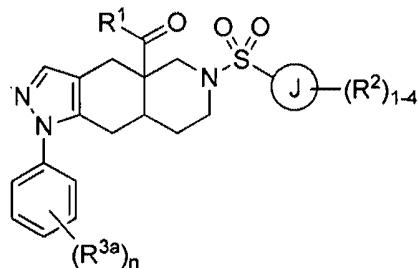
wherein R^{2G} is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, -CN, and -CF₃; J is phenyl; t is an integer from 0 to 5; X is -S(O₂)-; and R⁵ is phenyl optionally substituted with 1-5 R^{5A} groups, wherein R^{5A} is a member selected from hydrogen, halogen, -OR^{5A1}, S(O₂)NR^{5A2}R^{5A3}, -CN, and unsubstituted alkyl, wherein R^{5A1} is a member selected from hydrogen and unsubstituted alkyl, and R^{5A2} and R^{5A3} are members independently selected from hydrogen and unsubstituted alkyl, or salts and isomers thereof.

[00144] In some cases, the GRA having a non-steroidal backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin. In some cases, the heteroaryl ketone fused azadecalin has the formula:



[00145] wherein R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a} ; each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, N-oxide, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl; ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S; each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl- C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a} , $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 R^{2c} groups; alternatively, two R^2 groups linked to the same carbon are combined to form an oxo group ($=O$); alternatively, two R^2 groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2d} groups; R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; each R^{2c} is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, and $NR^{2a}R^{2b}$; each R^{2d} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, or two R^{2d} groups attached to the same ring atom are combined to form ($=O$); R^3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R^{3a} groups; each R^{3a} is independently selected from the group consisting of hydrogen, halogen, and C_{1-6} haloalkyl; and subscript n is an integer from 0 to 3; or salts and isomers thereof.

[00146] In some cases, the octahydro fused azadecalin has the formula:



[00147] wherein R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a} ; each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, N-oxide, and C_{3-8} cycloalkyl; ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S; each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl- C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a} , $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S; alternatively, two R^2 groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2c} groups; R^{2a} , R^{2b} and R^{2c} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; each R^{3a} is independently halogen; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

[00148] Further examples of non-steroidal glucocorticoid receptor antagonists include, for example N-(2-[4,4',4''-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4''-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4''-trichlorotrityl]imidazole); 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4',4''-trichlorotrityl)-1,2,4-triazole-3-thiol; 4 α (S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4 α ,9,10,10 α (R)-octahydro-phenanthrene-2,7-diol ("CP 394531"), 4 α (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4 α ,9,10,10 α (R)-octahydro-phenanthrene-2,7-

diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide, bremazocine, and ethylketocyclazocine.

[00149] As used herein, the term "hormone-sensitive cancer" refers to any cancer which may be affected by a hormone; hormones typically increase proliferation of hormone-sensitive cancers. Hormone sensitive cancers include, e.g., prostate cancer and other androgen-sensitive cancers; breast cancer, ovarian cancer and other estrogen-sensitive or progesterone-sensitive cancers.

[00150] As used herein, the term "chemotherapy" refers to medical treatments typically used to treat cancer. Chemotherapy treatments include the use of agents which are toxic to cancerous tissues and cells, or which act to slow or reduce the growth or spread of cancerous tissues and cells. Chemotherapy agents include antineoplastic agents and may be derived from natural compounds (e.g., taxols); may be, may mimic, or may reduce or block the actions of naturally occurring hormones, growth factors, or immunologically active molecules; may be synthetic small molecules; may be antibodies or antibody conjugates; and may be other agents. Exemplary chemotherapy agents include, but are not limited to, taxanes, taxol, docetaxel, paclitaxel, actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, bleomycin, cisplatin, trastuzumab (Herceptin[®]), trastuzumab emtastine (Kadcyla[®]), imatinib (Gleevec[®]), eribulin (Halaven[®]), among others known in the art.

[00151] As used herein, a phrase of the form "the reduced dose of Z is a dose that is at least about X% less than the original dose" (where "Z" represents a pharmaceutical compound or pharmaceutical composition, and "X" represents a numerical value) is used to indicate that the reduced dose is an amount of Z calculated by 1) multiplying the amount of Z in the original dose by X% to obtain a multiplicative product, and 2) subtracting that product from the original dose. Thus, for example, where the original dose is 600 mg, and X% is 50%, the multiplicative product of 600 mg and 50% is 300 mg, and the reduced dose is 300 mg; and, for example, where the original dose is 900 mg, and X% is 66%, the multiplicative product of 900 mg and 66% is about 600 mg (594 mg), and the reduced dose is about 300 mg (306 mg).

[00152] As used herein, the terms "pharmaceutical composition" and "formulation" refer to compositions suitable for administration to a patient for treatment of a medical condition or for amelioration of symptoms of a medical condition. A pharmaceutical composition as disclosed herein includes an active ingredient (e.g., a GRA, such as, e.g., mifepristone; or a combination of

a GRA and a SI, where the SI may be, e.g., ketoconazole) and a pharmaceutically acceptable excipient. In embodiments, a pharmaceutical composition includes one or more active ingredients and one or more pharmaceutically acceptable excipients.

[00153] As used herein, the terms “pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors, and the like. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[00154] As used herein, the terms “sustained release,” “slow release,” “long acting,” “prolonged release,” and the like refer to a pharmaceutical composition or formulation containing at least one active ingredient (*e.g.*, GRA, SI, or combination thereof) formulated to maintain a therapeutic concentration of active ingredient(s) in a patient for a longer period of time in comparison to formulations that are not designed for such sustained release. In some cases, the sustained release formulation maintains therapeutic concentration of one or more active ingredient(s) for, or for at least, one week, two weeks, three weeks, four weeks, five weeks, or six weeks. In some cases, the sustained release formulation is administered to a patient every one, two, three, four, five, or six weeks.

[00155] As used herein, a “steroidogenesis inhibitor” is a compound which reduces or blocks the synthesis of steroid molecules when administered to an animal, or subject, which normally produces steroids. Steroidogenesis inhibitors include, for example, ketoconazole, metyrapone, etomidate, and other drugs. A steroidogenesis inhibitor may act by one or more of several mechanisms, including, *e.g.*, blocking synthesis of steroid molecules (*e.g.*, ketoconazole, metyrapone).

[00156] As used herein, the term “CYP enzyme” refers to a cytochrome P450 enzyme. Cytochrome P450 enzymes are important in many metabolic and catabolic reactions in humans and other animals, and play important roles in drug metabolism and action. Drug-drug interactions in which administration of one drug affects the concentration, half-life, activity, or other effect of another drug may include effects on CYP enzymes by induction of CYP enzymes

(increasing the amount or activity of one or more CYP enzymes); inhibition (reducing the activity of one or more CYP enzymes); competition (competing for sites or occupying sites, e.g., as a substrate, of one or more CYP enzymes); or by other means. Particular CYP enzymes include, for example, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes.

[00157] As used herein, a “CYP3A inhibitor” is a compound which reduces or blocks the activity of the cytochrome CYP3A, or reduces or blocks the expression of the gene-product of CYP3A genes (e.g., inhibits transcription or translation of CYP3A genes). CYP3A inhibitors may be termed strong or moderate if their administration, along with a test drug known to be metabolized by CYP3A enzymes (such as, e.g., midazolam), raises the AUC (area under the concentration curve) of the test drug by greater than five-fold (strong CYP3A inhibitors) or by between two-fold and five-fold (moderate CYP3A inhibitors). Inhibitors of CYP3A include, for example, ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

[00158] Strong CYP3A inhibitors include, for example, ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, and voriconazole.

[00159] Metyrapone (also known as Metopirone[®]) is 2-methyl-1,2-bis-(3-pyridyl)-1-propanone. Metopirone is believed to reduce cortisol and corticosterone production by inhibiting the 11- β -hydroxylation reaction in the adrenal cortex.

[00160] Etomidate (also known as Amidate[®]) is R-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate. Although primarily used as a rapid-onset anesthetic, etomidate also lowers plasma cortisol levels. It is believed to reduce corticosteroid synthesis in the adrenal cortex by inhibiting 11 β -hydroxylase.

[00161] Ketoconazole (1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-- dioxolan-4-yl]methoxy]phenyl]piperazine) is often used to treat fungal infections (e.g., (NIZORAL[®]) for the treatment of fungal infections). In addition, ketoconazole is a steroidogenesis inhibitor and can reduce the production of steroid molecules (such as, e.g., steroid hormones), typically by blocking the metabolism of cholesterol. Ketoconazole thus may be used to treat excessive cortisol production (e.g., to treat Cushing’s disease and Cushing’s

syndrome), to reduce androgen production (e.g., in patients with hormone-sensitive cancers such as prostate cancer), to reduce estrogen or progesterone production (e.g., in patients with hormone-sensitive cancers such as breast cancer), and other treatments.

[00162] However, ketoconazole often has serious deleterious effects on liver and other organs. Thus, it is desirable to minimize the dose of ketoconazole administered to a patient, and methods for reducing the dose of ketoconazole are desired.

[00163] TREATMENT METHODS

[00164] Methods disclosed herein include methods of treating a disease characterized by excess steroid levels, or by excess activity due to steroids. Methods disclosed herein also include methods of treating a disease that may be treated by reducing or blocking the action of steroids, such as steroid hormones. In embodiments, the disease is characterized by excess cortisol levels, such as, e.g., Cushing's syndrome, and in particular, Cushing's Disease. (As noted above, both Cushing's syndrome and Cushing's Disease are characterized by excess cortisol; Cushing's Disease falls within the definition of Cushing's syndrome as a particular type or example of Cushing's syndrome; thus, all discussion and disclosure regarding Cushing's syndrome includes Cushing's Disease.) Methods disclosed herein also include methods of treating cancer and cancerous tumors, such as hormone-sensitive cancers including prostate cancer, comprising concomitant administration of a GRM and ketoconazole to provide thereby beneficial therapeutic effects. Methods, compositions, and kits disclosed herein are related to the methods compositions, and kits and compositions disclosed in U.S. Provisional Patent Application Serial No. 62/465,772, filed March 1, 2017, and U.S. Provisional Patent Application Serial No. 62/466,867, filed March 3, 2017, which applications are hereby incorporated by reference in their entireties.

[00165] For example, the present methods include concomitantly administering to a patient a CYP3A inhibitor and a glucocorticoid receptor modulator (GRM), such as a glucocorticoid receptor antagonist (GRA). In embodiments, the CYP3A inhibitor is ketoconazole. In embodiments, the CYP3A inhibitor is ketoconazole and the GRA is mifepristone. In embodiments, the patient is receiving a CYP3A inhibitor (such as, e.g., ketoconazole) and is concomitantly administered an amount of a GRA (such as, e.g., mifepristone) effective to treat Cushing's syndrome, e.g., effective to control hyperglycemia secondary to hypercortisolism in an adult patient suffering from endogenous Cushing's

syndrome. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitus or glucose intolerance. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome). In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitus or glucose intolerance and has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome).

[00166] In embodiments, the present methods include methods for treating Cushing's syndrome in a patient taking a GRA, comprising reducing the daily dosage amount of the GRA from an original GRA dose to an adjusted GRA dose when the patient is receiving concomitant administration of a CYP3A inhibitor. In embodiments, the adjusted dose of GRA is at least 25% less than the original dose. In embodiments, the adjusted dose of GRA is at least 33% less than the original dose. In embodiments, the adjusted dose of GRA is less than the original dose by a fraction of the original dose selected from 10%, 20%, 25%, 30%, 33%, 33^{1/3}%, and 50%. In embodiments, the GRA is mifepristone, and the adjusted mifepristone dose is selected from 300 mg per day, 600 mg per day, and 900 mg per day. In embodiments, the CYP3A inhibitor is ketoconazole. In embodiments, the CYP3A inhibitor is ketoconazole and the GRA is mifepristone. In embodiments, the patient is receiving a CYP3A inhibitor (such as, e.g., ketoconazole) and is concomitantly administered an amount of a GRA (such as, e.g., mifepristone) effective to treat Cushing's syndrome, e.g., effective to control hyperglycemia secondary to hypercortisolism in an adult patient suffering from endogenous Cushing's syndrome. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitus or glucose intolerance. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome). In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitus or glucose intolerance and has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome).

[00167] For example, the present disclosed methods include administering to a patient receiving ketoconazole an effective amount of a glucocorticoid receptor modulator (GRM), such as a glucocorticoid receptor antagonist (GRA). In embodiments, the patient is receiving

ketoconazole. In embodiments, the patient is receiving ketoconazole and the GRA is mifepristone. In embodiments, the patient is receiving ketoconazole and is administered an amount of mifepristone effective to reduce the effect of a steroid such as cortisol in the patient.

[00168] Thus, in embodiments, the methods disclosed herein include a method for treating a patient who is receiving ketoconazole treatment for excess steroid levels, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering a GRA to the patient receiving ketoconazole, whereby the patient receiving ketoconazole is administered a GRA for treating excess steroid levels. In embodiments, the GRA is mifepristone. In embodiments, the disease is Cushing's syndrome. In embodiments, the disease is Cushing's Disease.

[00169] Thus, in embodiments, the methods disclosed herein include a method for treating a patient who is receiving ketoconazole treatment to reduce or block the effects of steroids, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering a GRA to the patient receiving ketoconazole, whereby the patient receiving ketoconazole is administered a GRA for treating the effects of steroids in the patient. In embodiments, the GRA is mifepristone. In embodiments, the effects of steroids include hypercortisolemic effects, such as the effects of Cushing's syndrome. In embodiments, the effects of steroids include hormonal effects, such as effects on hormone-sensitive cancer.

[00170] Applicant further discloses a method for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering a GRA to the patient receiving ketoconazole, wherein the amount of GRA administered is a first dose of GRA, whereby the patient receiving ketoconazole is administered a GRA for treating Cushing's syndrome. In embodiments, the GRA is mifepristone. In embodiments, the Cushing's syndrome patient suffers from Cushing's Disease.

[00171] For example, the present disclosed methods include concomitantly administering to a patient in need thereof, a) an effective amount of a glucocorticoid receptor modulator (GRM), such as a glucocorticoid receptor antagonist (GRA), and b) an effective amount of ketoconazole, such as ketoconazole, thereby reducing the effect, the amount, or both, of steroids such as cortisol in the patient. For example, a Cushing's syndrome patient may be in need of

reducing their blood levels of cortisol, or may be in need of reducing the effect of cortisol in the patient. For example, a cancer patient may be in need of reducing their blood levels of a steroid, such as an androgen, a progestogen, an estrogen, or other steroid.

[00172] Thus, in embodiments of the methods disclosed herein, a subject currently receiving ketoconazole is administered a GRM. In embodiments of the methods disclosed herein, a subject currently receiving ketoconazole as treatment for a condition characterized by excess steroid levels, or as treatment of a condition that is treated by reducing steroid levels or by reducing steroid effects, is administered a GRM, whereby the subject is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is Cushing's syndrome. In embodiments, the condition is a cancer characterized by the deleterious action of steroid hormones on cells, such as cancer cells; the cancer may be hormone-sensitive cancer that may be treated by lowering the levels of a steroid in the patient. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

[00173] Accordingly, Applicant discloses herein a method for treating a patient in need of reduced steroid levels, the patient receiving an original dose of ketoconazole, said method comprising:
administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with said dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for reducing steroid levels in the patient. In embodiments of such methods, wherein said first dose of GRA comprises an amount of the GRA that is effective to aid in reducing steroid levels in the patient without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity.

[00174] Accordingly, Applicant discloses herein a method for treating a patient suffering from excess steroid levels, the patient receiving an original dose of ketoconazole, said method comprising:
administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with said dose of ketoconazole, whereby the

patient is administered both an original dose of ketoconazole and a first dose of a GRA for reducing steroid levels in the patient. In embodiments of such methods, wherein said first dose of GRA comprises an amount of the GRA that is effective to aid in reducing steroid levels in the patient without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity. In embodiments, the excess steroid comprises excess androgen. In embodiments, the excess steroid comprises excess progesterone. In embodiments, the excess steroid comprises excess estrogen. In embodiments, the excess steroid comprises excess cortisol.

[00175] Accordingly, in further embodiments, Applicant discloses herein methods for treating a Cushing's syndrome patient, the patient receiving an original dose of ketoconazole, said methods comprising:

administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with said dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for treating Cushing's syndrome. In embodiments of such methods, wherein said first dose of GRA comprises an amount of the GRA that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity.

[00176] In embodiments, Applicant discloses methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering said original dose of ketoconazole to said patient; and administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first dose of GRA comprises an amount of said GRA that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and a GRA for treating Cushing's syndrome and is not exposed to increased risk of ketoconazole toxicity. In embodiments, said GRA is mifepristone. In

embodiments, the original dose of ketoconazole and the first dose of GRA are administered within a short time of each other. In embodiments, the original dose of ketoconazole and the first dose of GRA are administered at substantially the same time. In embodiments, the original dose of ketoconazole and the first dose of GRA are administered concomitantly. In embodiments, the GRA is mifepristone.

[00177] Thus, in embodiments of these methods, administration of the ketoconazole and of the GRA comprises concomitant administration of the original dose of ketoconazole and the first dose of the GRA. In embodiments of concomitant administration, ketoconazole and the GRA are administered to the subject simultaneously. Such concomitant administration of a GRA may be by oral administration; by intravenous administration; subcutaneous administration; parenteral administration; intra-arterial administration; nasal administration; topical administration; or by other routes of administration, or combinations thereof.

[00178] In embodiments of the methods disclosed herein, ketoconazole and the GRA are administered to the patient in a single pill containing both the ketoconazole and the GRA, or are administered in a single liquid formulation containing both the ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

[00179] In embodiments of the methods disclosed herein, the first dose of the GRA is a dose selected from about 25 milligrams (mg), about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, and about 2000 mg. In embodiments, the dose of the GRA is a dose of mifepristone selected from about 300 mg, about 600 mg, about 900 mg, about 1200 mg, and about 1500 mg.

[00180] The methods disclosed herein include repeated administration of a GRA to a patient in need of treatment, including repeated concomitant administration of ketoconazole and a GRA.

[00181] For example, in yet further embodiments, a second dose of GRA is administered, wherein said second dose is administered after the administration of the first dose of GRA. The second dose of GRA may comprise about the same amount of said GRA as the first dose of the GRA; may comprise a greater amount of said GRA than the first dose of GRA; or may comprise a smaller amount of GRA than the first dose of GRA. In embodiments of these methods, the GRA is mifepristone.

[00182] The methods disclosed herein may further comprise: administering a subsequent dose of ketoconazole and a second dose of GRA, wherein said subsequent dose and said second dose are both administered after the administration of the first dose of the GRA. In embodiments, the second dose of GRA comprises about the same amount of the GRA as the first dose of GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments of these methods, the GRA is mifepristone.

[00183] In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA. In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of these methods, the GRA is mifepristone.

[00184] In embodiments comprising repeated administration of a GRA to a patient in need of treatment, including repeated concomitant administration of ketoconazole and a GRA, ketoconazole and the GRA may be administered simultaneously. In embodiments of such methods, the GRA may be mifepristone.

[00185] In embodiments, ketoconazole and a GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

[00186] Further embodiments of the methods disclosed herein may include further steps, e.g., may comprise administration of a third dose of a GRA, wherein said third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, such a third dose of GRA comprises about the same amount of the GRA as the second dose of the GRA. In embodiments, such a third dose of GRA comprises a greater amount of the GRA than the second dose of the GRA. In embodiments, such a third dose of GRA is administered after the administration of the second dose of the GRA. In embodiments, such a third dose of GRA comprises about the same amount of GRA as the amount of said second dose of the GRA. In embodiments, such a third dose of GRA comprises a lesser amount of the GRA than the amount of said second dose of the GRA. In embodiments, such a third dose of GRA comprises a greater

amount of the GRA than the amount of said second dose of the GRA. In such embodiments, the GRA may be mifepristone.

[00187] In embodiments, methods disclosed herein comprise concomitant administration of ketoconazole and a third dose of GRA. In embodiments of such concomitant administration, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of such concomitant administration, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

[00188] Embodiments of the methods disclosed herein comprise treatments for patients suffering from Cushing's syndrome; in embodiments, the Cushing's syndrome patient suffers from Cushing's Disease. Such treatments for Cushing's syndrome comprise concomitant administration of ketoconazole and a GRA to the patient.

[00189] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with ketoconazole and with a glucocorticoid receptor antagonist (GRA). In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with ketoconazole and a GRA, wherein the dose of ketoconazole administered concomitantly with the GRA is not reduced with respect to the ketoconazole dose administered to the patient in the absence of concomitant treatment with ketoconazole and a GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with a GRA and ketoconazole. In embodiments, the GRA is mifepristone.

[00190] Applicant discloses herein methods for treating a Cushing's syndrome patient, the patient receiving an original dose of ketoconazole, said method comprising: administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with the dose of SI, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for treating Cushing's syndrome. In embodiments, the patient suffers from Cushing's Disease.

[00191] In embodiments, Applicant discloses herein methods for treating a Cushing's syndrome patient, the patient receiving an original dose of ketoconazole, the method comprising:

administering a first dose of mifepristone to the patient, wherein the first mifepristone dose is administered concomitantly with the dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of mifepristone for treating Cushing's syndrome. In embodiments, the patient suffers from Cushing's Disease.

[00192] In further embodiments of such methods, wherein said first dose of a GRA comprises a GRA amount that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity. In embodiments, administration of ketoconazole and of the GRA comprises concomitant administration of the original dose of ketoconazole and the first dose of the GRA. In embodiments, administering a GRA comprises oral administration of the GRA. In embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

[00193] In embodiments of the methods disclosed herein, the first dose of the GRA is selected from about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, about 2000 mg, about 2100 mg, about 2400 mg, about 2700 mg, and about 3000 mg. In embodiments of the methods disclosed herein, the first dose of the GRA is a dose of mifepristone selected from about 1500 mg mifepristone, about 1200 mg mifepristone, about 900 mg mifepristone, about 600 mg mifepristone, and about 300 mg mifepristone.

[00194] Further embodiments of the methods disclosed herein comprise administering a second dose of GRA, wherein said second dose is administered after the administration of the first dose of GRA. In embodiments, the second dose of GRA comprises about the same amount of said GRA as the first dose of the GRA. In embodiments, the second dose of GRA comprises a greater amount of said GRA than the first dose of GRA. In embodiments, the GRA is mifepristone.

[00195] Further embodiments of the methods disclosed herein comprise administering a subsequent dose of ketoconazole and a second dose of GRA, wherein the subsequent

ketoconazole dose and the second GRA dose are both administered after the administration of the first dose of the GRA. In embodiments, the second dose of GRA comprises about the same amount of the GRA as the first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA. In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of the first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the GRA is mifepristone.

[00196] In embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments, the GRA is mifepristone. In embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments, ketoconazole and mifepristone are administered to the patient in a single pill containing both ketoconazole and mifepristone, or in a single liquid formulation containing both ketoconazole and mifepristone. In embodiments, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising both ketoconazole and mifepristone.

[00197] Embodiments of the methods disclosed herein further comprise administration of a third dose of GRA, wherein said third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, the third dose of GRA comprises about the same amount of the GRA as the second dose of the GRA. In embodiments, the third dose of GRA comprises a greater amount of the GRA than the second dose of the GRA. In embodiments, the methods further comprise administration of a third dose of GRA, wherein the third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, the third dose of GRA comprises about the same amount of GRA as the amount of

said second dose of the GRA. In embodiments, the third dose of the GRA comprises a lesser amount of the GRA than the amount of said second dose of the GRA. In embodiments, the third dose of GRA comprises a greater amount of the GRA than the amount of said second dose of the GRA. In embodiments, administration of the third GRA dose comprises concomitant administration ketoconazole and the third dose of GRA. In such embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of the methods comprising such third dose of GRA, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

[00198] Applicant discloses herein methods for treating Cushing's syndrome patients with a GRA (such as mifepristone) and ketoconazole. In embodiments, the patient suffers from Cushing's Disease.

[00199] Applicant discloses here methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering said original dose of ketoconazole to said patient; and administering a glucocorticoid receptor antagonist (GRA) to the patient, wherein the amount of GRA administered is a first dose of GRA, whereby the patient is administered both ketoconazole and a GRA for treating Cushing's syndrome. In embodiments, the first dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In embodiments, the GRA is mifepristone.

[00200] In embodiments of such methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the first dose of GRA comprises an amount of GRA that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity. In embodiments, the first dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In embodiments, the GRA is mifepristone.

[00201] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the administration of ketoconazole and of the GRA comprises concomitant administration of the original dose of ketoconazole and the first dose of said GRA.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the administration of the GRA comprises oral administration of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, ketoconazole and mifepristone are administered in a single liquid formulation comprising ketoconazole and mifepristone.

[00202] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the first dose of the GRA is a dose of GRA selected from about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, about 2000 mg, about 2100 mg, about 2400 mg, about 2700 mg, and about 3000 mg. In embodiments, the GRA is mifepristone, and the first dose of the GRA is a dose of mifepristone selected from about 1500 mg mifepristone, about 1200 mg mifepristone, about 900 mg mifepristone, about 600 mg mifepristone, and about 300 mg mifepristone.

[00203] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods further comprise: administering a second dose of GRA, wherein said second dose is administered after the administration of the first dose of said GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of GRA comprises about the same amount of said GRA as the first dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of GRA comprises a lesser amount of said GRA than the first dose of GRA. In embodiments, the second dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of GRA comprises a greater amount of said GRA than the first dose of GRA. In embodiments, the GRA is mifepristone.

[00204] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods further comprise: administering a subsequent dose of ketoconazole and a second dose of GRA, wherein the subsequent ketoconazole dose and the second GRA dose are both administered after the administration of the first dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of the GRA comprises about the same amount of the GRA as the first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the second dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole.

[00205] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of the GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of the GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation comprising ketoconazole and the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the GRA is mifepristone, and the ketoconazole and the mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

[00206] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods further comprise: administration of a third dose of

the GRA, wherein the third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, the third dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of GRA comprises about the same amount of the GRA as the second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises a greater amount of the GRA than the second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA is administered after the administration of the second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises about the same amount of GRA as the amount of said second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises a lesser amount of the GRA than the amount of said second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises a greater amount of the GRA than the amount of said second dose of the GRA. In embodiments, the GRA is mifepristone.

[00207] In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant administration of ketoconazole and of the third dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation comprising ketoconazole and the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the GRA is mifepristone, and the ketoconazole and the mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

[00208] In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with mifepristone and ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with mifepristone and ketoconazole, wherein the dose of ketoconazole administered concomitantly with ketoconazole is not reduced with respect to the ketoconazole dose administered to the patient in the absence of concomitant treatment with ketoconazole and mifepristone.

[00209] Applicant discloses herein a method for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering said original dose of ketoconazole to said patient; and administering mifepristone to the patient, wherein the amount of mifepristone administered is a first dose of mifepristone, whereby the patient is administered both ketoconazole and mifepristone for treating Cushing's syndrome. In embodiments, the first dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole.

[00210] In embodiments of methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, wherein the ketoconazole treatment comprises administering an original dose of ketoconazole to said patient, the methods comprise administering a first dose of mifepristone that comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of mifepristone and is not exposed to increased risk of ketoconazole toxicity. In embodiments of such methods, the administration of ketoconazole and of mifepristone comprises concomitant administration of the original dose of ketoconazole and of the first dose of mifepristone. In embodiments of such methods, the administration of mifepristone comprises oral administration of mifepristone. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone. In embodiments of such methods, the first dose of

mifepristone is a dose of about 300 milligrams (mg), about 600 mg, about 900 mg, about 1200 mg, or about 1500 mg.

[00211] In embodiments, such methods further comprise: administering a second dose of mifepristone, wherein said second dose is administered after the administration of the first dose of mifepristone. In embodiments, the second dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the first dose of mifepristone. In embodiments, such methods further comprise administering a subsequent dose of ketoconazole and a second dose of mifepristone, wherein said subsequent dose and said second dose are both administered after the administration of the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of such methods, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

[00212] In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered after the administration of the second dose of mifepristone. In embodiments, the third dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In

embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the second dose of mifepristone. In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered after the administration of the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a lesser amount of mifepristone than the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the amount of said second dose of mifepristone. In embodiments, such methods comprise concomitant administration of ketoconazole and of the third dose of mifepristone. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

[00213] In embodiments of methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment at an original dose of ketoconazole, the methods comprise administering a first dose of mifepristone to the subject and reducing the dose of ketoconazole received by the patient to a ketoconazole dose that is less than the original ketoconazole dose, wherein the dose of mifepristone comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of mifepristone and is not exposed to increased risk of ketoconazole toxicity.

[00214] Accordingly, Applicant discloses herein a method for treating a Cushing's syndrome patient who is receiving ketoconazole at an initial dosage, said initial dosage comprising administering an initial dose of ketoconazole to said patient, said method comprising: administering a reduced dose of ketoconazole to said patient, wherein said reduced dose of ketoconazole is a dose of ketoconazole that is less than said initial dose by an amount of at least about 5% of the initial dose; and administering mifepristone to the patient, wherein the amount

of mifepristone administered is a first dose of mifepristone, whereby the patient is administered both the reduced dose of ketoconazole and the first dose of mifepristone. In embodiments of such methods, the first dose of mifepristone comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome, whereby the patient is administered both a reduced dose of ketoconazole and an effective dose of mifepristone. In embodiments, the first dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the administration of ketoconazole and of mifepristone comprises concomitant administration of the reduced dose of ketoconazole and the first dose of mifepristone. In embodiments of such methods, the administration of mifepristone comprises oral administration of mifepristone. In embodiments of such methods, the first dose of ketoconazole is less than said initial dose of ketoconazole by an amount that is about 10%, about 15%, about 25%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 75%, or about 90% less than the initial dose. In embodiments of such methods, the first dose of mifepristone is a dose selected from about 300 mg, about 600 mg, about 900 mg, about 1200 mg, and about 1500 mg.

[00215] In embodiments, such methods further comprise administering a second dose of mifepristone, wherein said second dose is administered at a time after the administration of the first dose of mifepristone. In embodiments, the second dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises a lesser amount of mifepristone than the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the first dose of mifepristone. In embodiments, such methods further comprise administering a subsequent dose of ketoconazole and a second dose of mifepristone, wherein said subsequent dose and said second dose are both administered at a time after the administration of both the reduced dose of ketoconazole and of the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the reduced dose of ketoconazole. In embodiments of such methods, the subsequent dose of ketoconazole comprises

a lesser amount of ketoconazole than the amount of said reduced dose of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the reduced dose of ketoconazole.

[00216] In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered at a time after the administration of the second dose of mifepristone. In embodiments, the third dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the third dose of mifepristone comprises a lesser amount of mifepristone than the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the second dose of mifepristone.

[00217] In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered at a time after the administration of the second dose of mifepristone. In embodiments, the third dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a lesser amount of mifepristone than the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the amount of said second dose of mifepristone. In embodiments, such methods comprise administration of a dose of ketoconazole administered at the time as the administration of the third dose of mifepristone.

[00218] Applicant further discloses herein methods for treating a patient who is suffering from Cushing's syndrome with mifepristone, the patient also receiving concomitant administration of ketoconazole, said method comprising: to the patient concomitantly receiving ketoconazole, orally administering a dose of mifepristone that is a smaller dose of mifepristone

than the dose that is an effective mifepristone dose when the patient receives only mifepristone. An effective dose of mifepristone when the patient receives only mifepristone for treating Cushing's syndrome is termed a "lone dose" of mifepristone. For example, the dose of mifepristone that is effective for the treatment of a Cushing's syndrome patient not concomitantly receiving ketoconazole or other treatment for Cushing's syndrome is a "lone dose" of mifepristone. In embodiments of the methods disclosed herein, for Cushing's syndrome patient receiving concomitant administration of ketoconazole, the dose of mifepristone is reduced by at least about 5% as compared to the lone dose of mifepristone. Accordingly, Applicant discloses herein a method for treating a Cushing's syndrome patient who is receiving ketoconazole, said method comprising: administering a reduced dose of mifepristone to said patient, wherein said reduced dose of mifepristone is a dose of mifepristone that is less than the lone dose of mifepristone as defined herein; whereby the patient is administered both ketoconazole and the reduced dose of mifepristone. In embodiments, such a reduced dose of mifepristone is an amount of mifepristone that is less than the lone dose of mifepristone by an amount that is at least about 5% of the lone dose. In embodiments of such methods, the reduced dose of mifepristone comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome, whereby the patient is administered both a reduced dose of mifepristone and a dose of ketoconazole. In embodiments of such methods, the administration of ketoconazole and of mifepristone comprises concomitant administration of the reduced dose of mifepristone and the dose of ketoconazole. In embodiments of such methods, the administration of mifepristone comprises oral administration of mifepristone. In embodiments of such methods, the reduced dose of mifepristone is less than said lone dose of mifepristone by an amount that is about 10%, about 15%, about 25%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 75%, or about 90% less than the lone dose. In embodiments of such methods, the reduced dose of mifepristone is a daily dose selected from about 900 mg, about 600 mg, about 300 mg, or is a dose of mifepristone selected from about 300 mg mifepristone administered every other day, a dose of about 300 mg mifepristone administered every third day, and a dose of mifepristone of about 300 mg administered every fourth day.

[00219] COMPOSITIONS

[00220] Applicant discloses herein compositions comprising a glucocorticoid receptor antagonist (GRA) which may be used in the treatment of a patient suffering from excess cortisol,

e.g., in a patient suffering from Cushing's syndrome. In embodiments, the compositions comprising a GRA may be provided in an amount effective to control hyperglycemia secondary to hypercortisolism, and may be provided in an amount effective control hyperglycemia secondary to hypercortisolism in a patient suffering from endogenous Cushing's disease. In embodiments, the compositions comprising a GRA may be provided in an amount effective to control hyperglycemia secondary to hypercortisolism in a patient suffering from endogenous Cushing's disease, where the patient has failed surgery, or is not a candidate for surgery.

[00221] Applicant also discloses herein compositions comprising a glucocorticoid receptor antagonist (GRA) and ketoconazole. These compositions comprising a GRA and ketoconazole may be used in the treatment of a Cushing's syndrome patient.

[00222] The compositions as disclosed herein can be prepared in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The compositions of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compositions disclosed herein can be administered by inhalation, for example, intranasally. Additionally, the compositions of the present invention can be administered transdermally. The compositions disclosed herein can also be administered by intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995).

[00223] Accordingly, in embodiments disclosed herein, the compositions include pharmaceutical compositions including a pharmaceutically acceptable carrier or excipient, a glucocorticoid receptor antagonist (GRA), and a SI. SIs include, for example, ketoconazole, levoketoconazole, metyrapone, LCI699, aminoglutethimide, etomidate, LCI699 (Osilodrostat), and others.

[00224] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details

on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

[00225] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5% or 10% to 70% of ketoconazole and/or the GRA.

[00226] Suitable solid excipients include, but are not limited to, magnesium carbonate; magnesium stearate; talc; pectin; dextrin; starch; tragacanth; a low melting wax; cocoa butter; carbohydrates; sugars including, but not limited to, lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins including, but not limited to, gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[00227] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the invention can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain ketoconazole and/or the GRA mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, ketoconazole and/or the GRA may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[00228] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and ketoconazole and/or the GRA are dispersed

homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[00229] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[00230] Aqueous solutions suitable for oral use can be prepared by dissolving ketoconazole and/or the GRA in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[00231] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[00232] Oil suspensions can be formulated by suspending ketoconazole and/or the GRA in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by

the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[00233] The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be formulated for administration via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., *Gao Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., *Eyles, J. Pharm. Pharmacol.* 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.

[00234] In another embodiment, the compositions of the present invention can be formulated for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly comprise a solution of the compositions of the present invention dissolved in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known sterilization techniques. The formulations may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The

concentration of the compositions of the present invention in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

[00235] In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989).

[00236] ADMINISTRATION

[00237] The compositions disclosed herein can be delivered by any suitable means, including oral, parenteral and topical methods. Transdermal administration methods, by a topical route, can be formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[00238] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the GRA and ketoconazole. In embodiments, the GRA is mifepristone. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[00239] The GRA and ketoconazole can be co-administered or administered separately. Concomitant administration includes administering ketoconazole within 0.5, 1, 2, 4, 6, 8, 10, 12,

16, 20, or 24 hours of the GRA. Concomitant administration also includes administering the GRA and ketoconazole simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Moreover, the GRA and ketoconazole can each be administered once a day, or two, three, or more times per day so as to provide the preferred dosage level per day. In embodiments, the GRA is mifepristone.

[00240] In some embodiments, concomitant administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both the GRA and ketoconazole. Suitable co-formulations include single pharmaceutical compositions including a GRA, ketoconazole, and a pharmaceutically acceptable excipient. In embodiment, the GRA is mifepristone.

[00241] In other embodiments, the GRA and ketoconazole can be formulated separately.

[00242] Ketoconazole can be present in any suitable amount, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. Suitable dosage ranges for ketoconazole in combination with the GRA, include from about 0.1 mg to about 10,000 mg, or about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg. Suitable dosages for ketoconazole in combination with the GRA, include about 1 mg, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg. In embodiments, the GRA is mifepristone.

[00243] Similarly, the GRA can be present in combination with ketoconazole in any suitable amount. The amount of GRA can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. Suitable dosage ranges for the GRA in combination with the SI, include from about 0.1 mg to about 10,000 mg, or about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg. Suitable dosages for the GRA in combination with ketoconazole, include, but are not limited to, about 1 mg, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or about 1000 mg. In embodiments, the GRA is mifepristone,

[00244] Ketoconazole and the GRA can be present in the compositions of the present invention in any suitable weight ratio, such as from about 1:100 to about 100:1 (w/w), or about 1:50 to about 50:1, or about 1:25 to about 25:1, or about 1:10 to about 10:1, or about 1:5 to about 5:1 (w/w). Ketoconazole and the GRA can be present in any suitable weight ratio, such as about

1:100 (w/w), 1:50, 1:25, 1:10, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 25:1, 50:1 or 100:1 (w/w). Other dosages and dosage ratios of ketoconazole and the GRA are suitable in the compositions and methods disclosed herein. In embodiments, the GRA is mifepristone.

[00245] The composition can also contain other compatible therapeutic agents. The compounds described herein can be used in combination with one another, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[00246] KITS

[00247] Applicant further provides kits including compositions as disclosed herein. Kits may also include instructions for the use of the compositions.

[00248] In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole; and a pharmaceutical composition containing a GRA. In embodiments, the GRA is mifepristone.

[00249] In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole; and a pharmaceutical composition containing a GRA; and instructions for the use (e.g., administration) of the ketoconazole and the GRA. In embodiments, the GRA is mifepristone, and the instructions include instructions for the administration of mifepristone. In embodiments, the instructions include instructions regarding one or more of the number of pharmaceutical compositions to be taken each day, the timing of such administration, whether or not the pharmaceuticals are to be taken with food or in a fasted state, contraindications, possible side effects, activities to be avoided during treatment with the pharmaceutical compositions (if any), and foods to be avoided during treatment with the pharmaceutical compositions (if any).

[00250] In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole and a GRA. In embodiments, the GRA is mifepristone, and the pharmaceutical composition contains ketoconazole and mifepristone.

[00251] In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole and a GRA; and instructions for the use (e.g., administration) of the pharmaceutical composition. In embodiments, the GRA is mifepristone. In embodiments of the kits disclosed herein, the pharmaceutical composition includes ketoconazole and mifepristone, and the instructions include instructions for the administration of the pharmaceutical containing ketoconazole and mifepristone. In embodiments, the instructions include instructions regarding one or more of the number of pharmaceutical compositions to be taken each day, the timing of

such administration, whether or not the pharmaceutical composition is to be taken with food or in a fasted state, contraindications, possible side effects, activities to be avoided during treatment with the pharmaceutical composition (if any), and foods to be avoided during treatment with the pharmaceutical composition (if any).

[00252] EXAMPLES

[00253] The following examples are presented by way of illustration of embodiments of the methods disclosed herein, and serve to illustrate, but not to limit, the present disclosure of methods of treating patients suffering from Cushing's syndrome, including Cushing's Disease; or from prostate cancer and other androgen-sensitive cancers; or from breast cancer, ovarian cancer, or other cancer hormone-sensitive cancer (e.g., cancer sensitive to estrogen or progesterone); and patients suffering from other diseases, disorders, or syndromes.

[00254] EXAMPLE 1

[00255] A study was performed in order to determine the effect of oral ketoconazole at a dose of 400 mg once per day (OD) or 200 mg twice per day (BID) on the plasma pharmacokinetics of a 300 mg single dose of mifepristone given to a fasted subject, in comparison to previous study data. This study was an open-label study in healthy male subjects.

[00256] Healthy male volunteers between the ages of 18 to 45 years of age with a body mass index (BMI) ranging between 19 and 32 kg/m² and a weight of at least 60 kg (132 lbs) were enrolled. Subjects had no clinically significant abnormal findings on the physical examination, ECG, blood pressure, heart rate, medical history, or clinical laboratory results during screening. The QTc interval at screening was less than 450 msec.

[00257] In cohort 1, six subjects received ketoconazole 400 mg OD for 14 days. The cohort 1 subjects participated in a screening visit to assess eligibility, and in a check-in day during which eligibility was re-confirmed and the first dose of 400 mg oral ketoconazole given at approximately 8 PM (12 hours prior to expected time of Day 1 mifepristone dose).

[00258] The morning of Day 1, subjects received 400 mg oral ketoconazole fasted, 0.5 hour prior to receiving the 300 mg single dose of mifepristone fasted. Subjects remained in the clinic on Days 2 and 3 to receive 400 mg OD oral ketoconazole fasted, and for safety evaluation and collection of blood pharmacokinetic (PK) samples. Subjects were discharged from the clinic on Day 4 following administration of 400 mg OD oral ketoconazole fasted, and returned to the clinic the mornings of Days 5 through 13 to receive 400 mg OD oral ketoconazole fasted.

[00259] In cohort 2, six subjects received ketoconazole 200 mg BID for 14 days. The 300 mg single dose of mifepristone was given to all subjects on day 1. All 12 subjects completed the study. Cohort 2 subjects participated in a Screening visit to assess eligibility and a check-in Day (Day -1) during which eligibility was re-confirmed. On Day 0, subjects received 200 mg BID oral ketoconazole: the morning dose after an overnight fast and the evening dose 12 hours prior to expected time of Day 1 Mifepristone dose. The morning of Day 1, subjects received 200 mg oral ketoconazole fasted, 0.5 hour prior to receiving the 300 mg single dose of Mifepristone fasted. The evening of Day 1, subjects received 200 mg oral ketoconazole. Subjects remained in the clinic on Days 2, 3 and 4 to receive 200 mg BID oral ketoconazole, and for safety evaluation and collection of blood pharmacokinetic (PK) samples. Subjects were discharged from the clinic on Day 4 following evening administration of 200 mg oral ketoconazole, and returned to the clinic the morning and evening of Days 5 through 13 to receive 200 mg BID oral ketoconazole. Morning doses of ketoconazole on Days 0-13 were administered in the fasted state.

[00260] Subjects in both cohorts had blood sampling for determination of plasma concentrations of mifepristone and its metabolites within 30 minutes before mifepristone dosing and at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72 (Day 4), 120 (Day 6), 192 (Day 9), 264 (Day 12), and 336 (Day 15) post mifepristone dose. Subjects in both cohorts returned to the study center on Day 15 for safety monitoring, and completion of the Termination Visit procedures, followed by discharge from the study. Safety was assessed by spontaneously reported adverse events, physical examinations, and routine clinical laboratory tests. To the extent possible, any adverse events deemed study drug-related and that were ongoing at the time of discharge from the study were followed-up to resolution or until a determination is made that the unresolved event was stable.

[00261] No subject experienced a serious adverse effect (SAE), or an adverse event (AE) that resulted in discontinuation from the study. Three subjects (25%) experienced at least 1 treatment-emergent adverse event (TEAE). All TEAEs were mild in intensity. No TEAE was considered by the investigator to be related to mifepristone. One TEAE of insomnia was considered by the investigator to be related to ketoconazole.

[00262] Minimal changes in laboratory test results were observed during the course of the study. No laboratory test result was considered by the investigator to be a TEAE. Any abnormal

values or shifts from baseline were considered not clinically significant. No clinically significant changes in any electrocardiogram (ECG) parameter were observed.

[00263] Pharmacokinetics (PK): Blood samples were drawn within 30 minutes before mifepristone dosing and at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72 (Day 4), 120 (Day 6), 192 (Day 9), 264 (Day 12), and 336 (Day 15) post mifepristone dose. Pharmacokinetic parameters were calculated for plasma concentrations of mifepristone and its metabolites following the single dose at Day 1. Descriptive statistics (count, mean, median, standard deviation, minimum, maximum, and % coefficient of variation) were provided.

Mifepristone/metabolite concentrations were listed and summarized. Comparisons with previous study data were made. The mean PK parameters from this study are presented in Table 1 (“MIFE” indicates mifepristone). The abbreviations and symbols used in Table 1 have the following meanings: “Tmax” indicates time to maximum observed plasma concentration; “Tmin” indicates time to minimum observed concentration within the 24 hour dosing interval; “Cmax” indicates maximum observed plasma concentration; “Cmin” indicates minimum observed concentration within the 24 hour dosing interval; “Cavg” indicates average steady-state concentration and is defined as drug input rate (Ro) divided by drug removal rate (CLss) ($C_{avg} = Ro / CL_{ss}$, where f (the fraction absorbed) cancels out (f is a factor of both Ro and CLss); this equation reduces to $C_{avg} = AUC_{tau}/tau$); “AUC0-24” indicates area under the plasma concentration versus time curve from time 0 to 24 hours post-dose, calculated using the linear trapezoidal rule (this is the same as AUCtau where tau is 24 hours or 1 day); “%Fluct” indicates percent fluctuation in drug concentrations at steady-state computed as $\%Fluct = 100 \times (C_{max} - C_{min})/C_{avg}$.

[00264] PHARMACOKINETIC (PK) RESULTS: Mifepristone plasma concentrations showed a rapid initial decline followed by a slow decline over time. At later time points, concentrations showed an accelerated decline indicative of non-linear kinetics. Metabolites peaked later relative to parent mifepristone as would be expected. Mifepristone metabolite RU 42633 exposure was similar or even greater than that for mifepristone, while RU 42698 (a mifepristone metabolite) exposure was approximately 0.74 to 0.94 relative to mifepristone and RU 42848 (also a mifepristone metabolite) exposure was 0.53 to 0.68 relative to mifepristone. With increase in time interval, the fraction of AUC relative to mifepristone accounted for by metabolite increased.

[00265] Cohort 2 C_{max} (where C_{max} is the maximum observed plasma concentration) and AUC_{inf} (where AUC_{inf} is the area under the concentration-time curve from time of last dose to infinity) were similar to corresponding parameters in Cohort 1. The geometric mean ratio (GMR) for C_{max} was 1.15 and that for AUC_{inf} was 1.05. However, the 90% confidence intervals around the GMR were higher than the standard 80:125 reference interval. Thus, there may be a small increase in mifepristone exposure with a divided ketoconazole dose (200 mg BID vs. 400 mg OD), but this was minor. Terminal half-life was approximately the same in Cohort 2 versus Cohort 1 and T_{max} was shorter for Cohort 2 versus Cohort 1.

[00266] SAFETY RESULTS: Among 12 subjects who received mifepristone, 3 (25%) experienced at least one treatment emergent adverse event (TEAE). All TEAEs were mild in intensity. No TEAE was considered by the investigator to be related to Mifepristone. One TEAE of insomnia was considered by the investigator to be related to ketoconazole. No subject experienced an SAE or an AE that resulted in discontinuation from the study. Minimal changes in laboratory test results were observed for subjects during the course of the study. No laboratory test result was considered by the investigator to be a TEAE. Any abnormal values or shifts from Baseline values were considered not clinically significant. No clinically significant changes in any ECG parameter were observed.

[00267] While PK parameters in Cohort 2 were similar to those in Cohort 1, the 90% confidence intervals around the GMR were higher than the standard 80:125 reference interval used for bioequivalence testing. Thus, there may be a small and minor increase in mifepristone exposure with a divided ketoconazole dose (200 mg BID vs. 400 mg OD). Terminal half-life was approximately the same in Cohort 2 versus Cohort 1 and T_{max} was shorter for Cohort 2 versus Cohort 1. Mifepristone 300 mg was safe and well tolerated in healthy volunteers under the following treatment regimens: single-dose fasted with ketoconazole 400 mg OD for 14 days or ketoconazole 200 mg BID for 14 days.

[00268] EXAMPLE 2

[00269] The primary objective of this study was to determine the effect of a 400 mg single dose of ketoconazole on the PK of an 8-day regimen of 300 mg or 600 mg OD mifepristone given following a moderate fat (34%) breakfast. This was an open-label study in healthy male subjects. In cohort 1, six subjects received mifepristone 300 mg OD for 8 days. In cohort 2, six subjects received mifepristone 600 mg OD for 8 days. The 400 mg single dose of

ketoconazole was given to all subjects on day 8. Three subjects discontinued early from the study: one subject in cohort 1 due to new onset sinus bradycardia, and two subjects in cohort 2 due to withdrawn consent.

[00270] **METHODOLOGY:** Twelve subjects were enrolled, six in Cohort 1 and 6 in Cohort 2. Three subjects discontinued early from the study, one subject in Cohort 1 due to an adverse event of sinus bradycardia, and two subjects in Cohort 2 due to withdrawn consent.

[00271] **Cohort 1:** Subjects participated in a Screening visit to assess eligibility, and returned to the clinic on Days 1-6 to receive 300 mg oral mifepristone following a moderate fat breakfast. On Day 7 subjects were admitted to the clinic in the fasted state for a pre-dose PK blood draw, after which they received 300 mg oral mifepristone following a moderate fat breakfast. Subjects had serial blood sampling for determination of mifepristone and its metabolites at hours 0.5, 1, 2, 4, 6, 8, and 12 post Day 7 dose. On Day 8, a pre-dose PK sample was drawn within 30 minutes prior to ketoconazole dosing for determination of plasma concentrations of mifepristone and its metabolites and ketoconazole. Following a moderate fat breakfast on Day 8, subjects received 400 mg ketoconazole 0.5 hours prior to 300 mg mifepristone and had serial blood sampling at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 120 post mifepristone dose for determination of plasma concentrations of mifepristone and its metabolites; and at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 post ketoconazole dose for determination of plasma concentrations of ketoconazole. Subjects were discharged on Day 11.

[00272] **Cohort 2:** Subjects participated in a Screening visit to assess eligibility and returned to the clinic on Days 1-6 to receive 600 mg oral mifepristone following a moderate fat breakfast. On Day 7 subjects were admitted to the clinic in the fasted state for a pre-dose PK blood draw, after which they received 600 mg oral mifepristone following a moderate fat breakfast. Subjects had serial blood sampling for determination of mifepristone and its metabolites at hours 0.5, 1, 2, 4, 6, 8, and 12 post Day 7 dose. On Day 8, a pre-dose PK sample was drawn within 30 minutes prior to ketoconazole dosing for determination of plasma concentrations of mifepristone and its metabolites and ketoconazole. Following a moderate fat breakfast on Day 8, subjects received 400 mg ketoconazole 0.5 hours prior to 600 mg mifepristone and had serial blood sampling at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 120 post mifepristone dose for determination of plasma concentrations of mifepristone and its metabolites; and at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 post ketoconazole dose for

determination of plasma concentrations of ketoconazole. Subjects were discharged on Day 11. Subjects in both cohorts returned to study center on Day 13 for safety monitoring, collection of the 120-hour PK draw, and completion of the Termination Visit procedures, followed by discharge from the study. To the extent possible, any adverse events deemed study drug-related and that were ongoing at the time of discharge from the study were followed-up to resolution or until a determination was made that the unresolved event was stable.

[00273] DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy male volunteers between the ages of 18 to 45 years of age with a body mass index (BMI) ranging between 19 and 32 kg/m² and a weight of at least 60 kg (132 lbs) were enrolled. Subjects had no clinically significant abnormal findings on the physical examination, ECG, blood pressure, heart rate, medical history, or clinical laboratory results during screening. The QTc interval at screening was less than 450 msec.

[00274] DURATION OF TREATMENT: Up to a total of 28 days, including up to 2 weeks screening, dosing on Days 1-8, safety observation, and PK sample collection through Day 13. For measuring the pharmacokinetics of mifepristone, samples were collected within 30 minutes before Day 7 mifepristone dose and at hours 0.5, 1, 2, 4, 6, 8, and 12 post Day 7 mifepristone dose; within 30 minutes before Day 8 ketoconazole dosing and at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 120 post Day 8 mifepristone dose. For measuring the pharmacokinetics of ketoconazole, samples were collected predose on Day 8 (24 hr sample from Day 7), and at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post ketoconazole dose.

[00275] Safety was assessed by spontaneously reported adverse events, physical examinations, and routine clinical laboratory tests. Adverse event data were tabulated. Physical findings and laboratory test results were listed by subject.

[00276] SAFETY RESULTS: No subject experienced an SAE. Among twelve subjects who received mifepristone, six subjects (50%) experienced at least 1 TEAE. TEAEs were predominantly mild in intensity. The majority of subjects (5/6) with TEAEs were in Cohort 2 and onset of the majority of TEAEs occurred on or after Day 8 during treatment with both ketoconazole and mifepristone 600 mg. TEAEs considered possibly or probably related to mifepristone administration in four subjects in Cohort 2 were dizziness, nausea, vomiting, dry mouth, and rash. One TEAE of headache was considered by the investigator to be possibly related to both ketoconazole and mifepristone administration. One subject in Cohort 1 with a

TEAE of nodal arrhythmia on Day 8 was withdrawn by the investigator. The event was considered mild in severity and not considered related to study medication. The corresponding ECG abnormality noted as “sinus bradycardia” was considered not clinically significant. No subject experienced an SAE.

[00277] Minimal changes in laboratory test results were observed for subjects during the course of the study. No laboratory test result was considered by the investigator to be a TEAE. There were no clinically significant changes or abnormalities in vital signs, physical examinations or body weights during the study. Abnormal ECGs occurred in four subjects and no abnormality was considered clinically significant.

[00278] STATISTICAL METHODS: Pharmacokinetics (PK): Pharmacokinetic parameters C_{max}, C_{trough}, and interdosing interval AUC were calculated for plasma concentrations of mifepristone and its metabolites following dose on Days 7 and 8. Descriptive statistics (count, mean, median, standard deviation, minimum, maximum, and % coefficient of variation) were provided. mifepristone/metabolite concentrations were listed and summarized. GM means of C_{max} and AUC₀₋₂₄ were compared for Day 8 to Day 7 in this study and also to combined data of 300 mg OD mifepristone in previous multiple dose studies. Additionally, comparisons were made between the PK results of cohort 1 and 2. Pharmacokinetic parameters C_{max}, T_{1/2} and total AUC were calculated for plasma concentrations of ketoconazole following the single dose on Day 8. Descriptive statistics (count, mean, median, standard deviation, minimum, maximum, and % coefficient of variation) were provided. Ketoconazole concentrations were listed and summarized. GM means of C_{max} and total AUC were compared for the single dose in this study to the combined data of reported 400 mg single doses of ketoconazole of healthy subjects from the literature.

[00279] The mean (\pm SD) age of subjects was 29.4 \pm 6.8 years, and the mean BMI at screening was 25.61 \pm 3.27 kg/m². Seven of twelve subjects (58.3%) were White, and 5/12 (41.7%) were Black/African American. Five of the 12 subjects (41.7%) were of Hispanic or Latino ethnicity.

[00280] PHARMACOKINETIC (PK) RESULTS: PK data for mifepristone and metabolites was available for eleven of the 12 enrolled subjects and data for ketoconazole PK analyses was available for 10 subjects. Concentrations of mifepristone and each metabolite were above the limits of detection during the entire sampling duration from Day 7 predose to Day 13

(end of study). mifepristone plasma concentrations showed a rapid initial decline followed by a slow decline over time and metabolites peaked later relative to parent mifepristone as expected. Mean RU 42633 and RU 42848 exposure was similar or even greater than that for mifepristone, while RU 42698 exposure was lower. Ketoconazole PK after a single dose on Day 8 was readily computed. Co-administration of ketoconazole increased mifepristone and metabolite exposure. In the presence of 400 mg ketoconazole on Day 8, Cohort 1 mifepristone C_{max} and AUC₀₋₂₄ increased by 20% and 25% relative to the prior Day 7 without ketoconazole. This effect was slightly greater at 600 mg OD mifepristone in Cohort 2, where C_{max} and AUC₀₋₂₄ increased by 39% and 28% between Day 7 and Day 8. A dose of 600 mg OD mifepristone (Cohort 2) resulted in higher mifepristone and metabolite exposure relative to a dose of 300 mg OD (Cohort 1) both alone and in the presence of 400 mg ketoconazole. This increase was less than proportionate to the two-fold dose increment. On Day 7 without ketoconazole, mifepristone C_{max} and AUC₀₋₂₄ at 600 mg OD were 42% and 48% greater than at 300 mg OD. This dose effect was greater in the presence of 400 mg ketoconazole. Day 8 mifepristone C_{max} and AUC₀₋₂₄ were 65% and 52% greater at 600 mg OD than at 300 mg OD. mifepristone half-life on Day 8 in the presence of 400 mg ketoconazole was similar between the two mifepristone dose levels. Day 8 half-life was 13% greater at 600 mg OD than at 300 mg OD. Ketoconazole exposure following a single 400 mg dose on Day 8 of a regimen of 600 mg OD mifepristone was 37% and 36% higher (C_{max} and AUC_{inf}) relative to a mifepristone regimen of 300 mg OD. Ketoconazole half-life on either mifepristone regimen was not appreciably different. The addition of a single dose of 400 mg ketoconazole to 300 mg or 600 mg OD mifepristone on Day 8 resulted in exposure increases in C_{max} and AUC₀₋₂₄ that were similar to historical values at 600 mg or 1200 mg OD in the fasted state and 1200 mg OD in the fed state, respectively. Although the increase in exposure due to the addition of ketoconazole was only between 20% and 39% in absolute terms, the resulting exposure was similar to that of a dose 2 to 3 times greater. This is believed to be due to a lack of dose-proportional kinetics for mifepristone.

[00281] The mean PK parameters and results from this study are presented in Table 2.

[00282] The abbreviations and symbols used in Table 2 have the following meanings:

[00283] “T_{max}” indicates time to maximum observed plasma concentration; “T_{min}” indicates time to minimum observed concentration within the 24 hour dosing interval; “C_{max}” indicates maximum observed plasma concentration; “C_{min}” indicates minimum observed

concentration within the 24 hour dosing interval; “Cavg” indicates average steady-state concentration and is defined as drug input rate (Ro) divided by drug removal rate (CLss) ($C_{avg} = R_o / CL_{ss}$, where f cancels out; this equation reduces to $C_{avg} = AUC_{tau}/tau$); “AUC0-24” indicates area under the plasma concentration versus time curve from time 0 to 24 hours post-dose, calculated using the linear trapezoidal rule (this is the same as AUCtau where tau is 24 hours or 1 day); “%Fluct” indicates percent fluctuation in drug concentrations at steady-state computed as $\%Fluct = 100 \times (C_{max} - C_{min})/C_{avg}$.

[00284] Drug-drug interaction (DDI) effects of ketoconazole on mifepristone and of mifepristone on ketoconazole were studied. A single 400 mg dose of ketoconazole caused a detectable increase in mifepristone exposure at mifepristone doses of 300 and 600 mg OD, and mifepristone at these doses caused a detectable increase in ketoconazole exposure. Although the increase in mifepristone exposure due to the addition of ketoconazole was only between 20% and 39% in absolute terms, the resulting exposure was similar to that of a dose 2 to 3 times greater. This is believed to be due to a lack of dose-proportional kinetics for mifepristone. Predominantly mild AEs occurred and were observed primarily in subjects administered ketoconazole and mifepristone 600 mg.

[00285] EXAMPLE 3

[00286] A Phase 1, single-center, open-label study was performed to study the effect of oral twice-daily doses of 200 mg of ketoconazole given with multiple oral once-daily doses of 600 mg of mifepristone in healthy male volunteers, during which all drug administrations were given after a typical meal (34% fat content). An objective of this study was to determine the effect of ketoconazole 200 mg twice daily on the PK of mifepristone 600 mg once daily when both drugs were administered with food. A single dose of ketoconazole was administered on Day -1. During multidose administration, mifepristone was administered on Days 1-17 and ketoconazole on Days 13-17; follow-up continued on Days 18-31. Sixteen subjects were enrolled (mean age 31.9 years; 8 black, 6 white, 2 other), and two subjects discontinued before starting the mifepristone/ketoconazole combination treatment.

[00287] The study was a two period study design. In Period 1: 600 mg mifepristone was administered once daily from Day 1 to Day 12; pharmacokinetic samples were taken before each dose for assay of mifepristone and active metabolites (mono-demethylated metabolite, RU 42633; hydroxylated metabolite, RU 42698; and di-demethylated metabolite, RU 42848) to

confirm that steady-state was achieved, and for a dose-interval concentration-profile on Day 12. In Period 2: 600 mg mifepristone once daily was continued in combination with 200 mg ketoconazole twice daily from Days 13 to 17; pharmacokinetic samples were taken for assay of both mifepristone and metabolites, and ketoconazole before dosing on Days 13 to 17, and on Day 17 for a dose-interval concentration-time profile

[00288] A secondary objective was to determine if the effect of 200 mg BID ketoconazole on the PK of co-administered 600 mg OD mifepristone at steady-state exceeded exposure to mifepristone and metabolites compared to that of 1200 mg OD mifepristone with food, the labeled dosing regimen with the highest mean observed exposure in healthy subjects.

[00289] Effects of Co-Administration with Ketoconazole on Mifepristone and Metabolites: The concentrations of mifepristone and the hydroxylated metabolite, RU 42698, were higher on Day 17 (600 mg mifepristone daily co-administered with 200 mg ketoconazole twice daily) than on Day 12 (mifepristone alone). Concentrations of RU 42633 and RU 42848 were similar on Day 17 and Day 12. Results of the formal statistical analysis are shown in Table 3.

[00290] For mifepristone, the geometric mean ratio of test to reference for C_{max} was 127.59% (90%CI: 116.66, 139.54, where "CI" means "confidence interval" and "90%CI" means "90% confidence interval") and for AUC_{0-24} was 138.01% (90%CI: 127.12, 149.84). The lower bound of the 90% confidence intervals exceeded 100% and the upper bound exceeded 125%. Thus, co-administration with ketoconazole increased mifepristone exposure. Similarly, for metabolite RU 42698, the lower bounds of the 90% confidence intervals exceeded 100% and both geometric mean ratios and the upper bound of the 90% confidence interval exceeded 125%, and thus exposure to this metabolite was increased by ketoconazole.

[00291] For metabolites RU 42848 and RU 42633, the calculated geometric mean ratios and 90% confidence intervals of exposure ratios were within the standard 80:125 comparison interval and thus not affected by ketoconazole.

[00292] Effects of Co-administration with mifepristone on Ketoconazole: The plasma concentration-time profiles of ketoconazole given twice daily with mifepristone on Day 17 were much higher than for ketoconazole given as a single dose alone on Day -1. Results of the formal statistical analysis are shown in Table 4.

[00293] The geometric mean ratio of test to reference for C_{max} was 252.71% (90%CI: 214.85, 297.26) and for AUC was 365.36% (90%CI: 333.78, 399.93). Thus, the geometric mean ratio and both lower and upper bounds of the 90% confidence intervals were entirely above the standard 80:125 comparison interval and exposure on Day 17 (with mifepristone) was higher than on Day -1 (ketoconazole alone).

[00294] Comparison of Mifepristone Exposure with mifepristone Labeled Doses: The concentration-time plots showed that mean mifepristone concentrations on Day 17 in the present study were less than those in the fed condition in a previous “historic” study in which subjects received 1200 mg mifepristone daily for seven days. Mifepristone was administered to the subjects within thirty minutes following a typical meal (34% fat) in both the present study and in the historic study. Results of the formal statistical analysis are shown in Table 5.

[00295] For mifepristone, the geometric mean ratio of test to reference for C_{max} was 84.64% (90% CI: 72.92, 98.23); for AUC_{0-24} it was 87.27% (90% CI: 74.72, 101.94). The 90% confidence intervals were below and overlapping the standard 80:125 comparison interval. The mean mifepristone concentrations in subject receiving 600 mg mifepristone following a 34% fat meal were less than the mifepristone concentrations in the historic study. As shown in Table 5, administration of 600 mg mifepristone in the fed state with ketoconazole resulted in mifepristone concentrations that were less than the mifepristone concentrations measured in subjects receiving 1200 mg mifepristone daily in the absence of ketoconazole. The Geometric Mean Ratio (GMR) values in Table 5 suggest that mifepristone 600 mg co-administered with ketoconazole yields mifepristone exposure 13-15% less than that of 1200 mg mifepristone in the absence of ketoconazole; for the metabolites, corresponding values range from an 18-19% decrease to a 17-18% increase. Thus, administration of 600 mg mifepristone daily with ketoconazole resulted in mifepristone concentrations that were not higher than the mean observed exposure at 1200 mg mifepristone; both treatments given following typical 34% fat meal. The value of 87% for GMR of the AUCs suggests that 900 mg mifepristone in the presence of ketoconazole would better match the exposure of a subject to 1200 mg mifepristone alone than would 600 mg mifepristone in the presence of ketoconazole. Thus, these data also support the use of 900 mg mifepristone, and higher doses as well, in the presence of ketoconazole.

[00296] For metabolite RU 42633, the 90% confidence intervals were within the standard interval for C_{max} (geometric mean ratio 96.31%) and just overlapping the lower bound of the

standard interval for AUC_{0-24} (geometric mean ratio 91.34%). For metabolite RU 42698, confidence intervals for both C_{max} and AUC_{0-24} were overlapping and above the standard interval (geometric mean ratio C_{max} : 116.55%; AUC_{0-24} : 118.18%). For metabolite RU 42848, the 90% confidence intervals were overlapping and below the standard interval for C_{max} (geometric mean ratio 82.45%) and AUC_{0-24} (ratio 81.43%).

[00297] RU 42698 is a relatively minor metabolite and comprises 9 % of the total steady-steady AUC_{0-24} of mifepristone, RU42633, RU42698, RU42848 alone and 13 % of the total steady-steady AUC_{0-24} in the presence of ketoconazole. Therefore, the increase in RU 42698 AUC_{0-24} in the presence of ketoconazole is considered to be minor.

[00298] Fig. 1 illustrates the results of measurements of plasma levels of mifepristone, RU42633, RU42698, and RU 42848. These measurements were made prior to the daily administration of mifepristone to the subject; thus the mifepristone and metabolite concentrations are “trough” concentrations. These results show that trough concentrations of mifepristone and RU42848 were increasing day-by-day through the start of ketoconazole administration (Day 13). This indicates that steady state conditions may not have been attained at the time of ketoconazole administration (which began on day 13).

[00299] Fig. 2 shows the plasma concentration profile of mifepristone before and after inhibition of CYP3A by ketoconazole. Applicant notes that the time 0 values (pre-dose) differ by ~ 500 ng/ml, a difference that is maintained relatively constant throughout much of the 24-hour sampling interval. Thus, if the daily increase in trough concentrations between days 7 and 12 persevered through day 17, an unknown fraction of the increased AUC (and C_{max}) between Day 12 and Day 17 could be due to further mifepristone administration rather than by an effect of ketoconazole alone. Thus, the values reported in Table 3 may overstate the impact of CYP3A inhibition on exposure to mifepristone (and RU42848).

[00300] CONCLUSIONS: Co-administration of 600 mg mifepristone once daily with 200 mg ketoconazole twice daily resulted in a mean increase in exposure to mifepristone of approximately 28% (C_{max} : geometric mean ratio 127.59% [90% CI: 116.66, 139.54]) and 38% (AUC_{0-24} : geometric mean ratio 138.01% [90%CI: 127.12, 149.84]). These exposures are approximately 85% of those observed following the highest labeled dose of mifepristone (1200 mg daily).

[00301] The mean increase in exposure to the hydroxylated metabolite, RU 42698 (approximately 70%), was somewhat greater than the increase in exposure to parent, resulting in exposure that was approximately 15 to 20% higher than that following the highest labeled dose of mifepristone. In contrast, co-administration with ketoconazole resulted in little change in exposure to the mono-demethylated metabolite, RU 42633, or di-demethylated metabolite, RU 42848; exposure to these metabolites was similar to or slightly lower than exposure following the highest labeled dose.

[00302] The results presented in this example indicate that, with inhibition of CYP3A (e.g., by co-administration of a strong CYP3A inhibitor such as ketoconazole), a subject previously administered 1200 mg mifepristone daily would experience corresponding increases in mifepristone C_{max} and AUC of 27.59% and of 38.01%, respectively, which should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily. Thus, the results of these measurements indicate that a subject, previously receiving a dose of 1200 mg mifepristone daily, may be safely administered a dose of 900 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen. Similarly, the results of these measurements indicate that a subject, previously receiving a dose of 900 mg mifepristone daily, may be safely administered a dose of 600 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen. In addition, the results of these measurements indicate that a subject, previously receiving a dose of 600 mg mifepristone daily, may be safely administered a dose of 300 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen.

[00303] No deaths or SAEs were reported during the study. Two subjects discontinued due to AEs (moderate hypertension in one subject and moderate bilateral rash on the upper arms and thighs in the other subject, both during the mifepristone-only treatment period). At least one TEAE was reported in 55.6% (9 of 16) of the subjects during treatment with mifepristone alone, in 57.1% (8 of 14) of the subjects during the mifepristone/ketoconazole treatment period, and in 7.1% (1 of 14) of the subjects during the washout period.

[00304] The majority of TEAEs were mild. Four subjects reported moderate TEAEs: three subjects during treatment with mifepristone alone (1 each reporting hypertension, rash, and vomiting) and 1 subject during treatment with mifepristone/ketoconazole (headache). All four moderate AEs were considered possibly or probably related to mifepristone treatment. Only 1 of

the moderate AEs was considered to be possibly related to ketoconazole treatment. No severe TEAEs were reported.

[00305] Three subjects had elevated laboratory test results that were reported as drug-related TEAEs. Mildly elevated liver enzymes were noted for one subject starting on the morning of Day 14, and mildly elevated creatinine levels were noted for two subjects starting on the morning of Day 14. Dosing was not interrupted for any of the subjects, and the events resolved without sequelae.

[00306] No clinically significant effects of multiple-dose mifepristone treatment with or without multiple-dose ketoconazole treatment were observed on hematology or urinalysis parameters, vital signs, or ECGs.

[00307] Example 4

[00308] The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 1200 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 900 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

[00309] Example 5

[00310] The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 900 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 600 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

[00311] Example 6

[00312] The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 600 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 300 mg, so that the patient

receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

[00313] Example 7

[00314] The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 1500 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 1200 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

[00315] All patents, patent applications, and publications identified herein are hereby incorporated by reference herein in their entireties.

Product ID/ Batch No. (NME)	Study Objective	Study Design	No. Subjects Enter/ Complete (M/F)	Age: Mean Range	Treatments		MIFEPRISTONE Mean PK Parameters (SD)					Mean Ratio Confidence Interval	
					Substrate	Interacting Drug	C _{max} ng/mL	T _{max} h	AUC _{tot} ng·h/mL	AUC _t ng·h/mL	T _{1/2} h	C _{max} ng/mL	AUC _{total} ng·h/mL
Mifepristone 300 mg Tablet Keto 200 mg Tablet	Effect of ketoconazole 400 mg OD (or 200 mg BID) on PK of 300 mg single dose Mifepristone given fasted	Phase 1, open-label, parallel group, single MIFE dose, multiple keto doses, in healthy subjects	12/12 (12 M)	28 20-44	MIFE 300 mg C1	400 mg/d Keto 400 mg OD	3398 (6.77)	median 2.00	116939 (26850)	38111 (8768)	37.1 (9.77)	1.15 0.81- 1.63 (C2/C1)	1.05 0.72-1.54 (C2/C1)
					MIFE 300 mg C2	400 mg/d Keto 200 mg BID	4143 (1736)	median 1.00	130925 (60942)	40625 (16524)	37.4 (18.5)		

MIFE = mifepristone, Keto = ketoconazole, AUC_{tot} = AUC_{total},
AUC_t = AUC₀₋₂₄ hours following single dose of MIFE
C1 = Cohort 1, C2 = Cohort 2

TABLE 1

Product ID/ Batch # (NME)	Study Objective	Study Design	# Subjects Enter/ Complete (M/F)	Age: Mean Range	Treatments		MIFEPRISTONE Mean PK Parameters (SD)					Mean Ratio Confidence Interval	
					Substrate	Interacting Drug	C _{max} ng/mL	T _{max} h	AUC _{tot} ng·h/ mL	AUC _t ng·h/ mL	T _{1/2} h	C _{max} ng/mL	AUC _t ng·h/mL
Mifepristone 300 mg Tablet Keto 200 mg Tablet	Effect of 400 mg single dose of ketoconazole on PK an 8 day regimen of 300 mg OD Mifepristone (or 600 mg OD Mifepristone) given with moderate fat (34%) breakfast	Phase 1, open-label, parallel group, crossover within group with multiple MIFE doses, and single keto dose, in healthy subjects	12/10 (12 M)	29.8 20-43	MIFE 300 mg/d C1 Day 7		2700 (534)	median 3.0	NC ^a	37734 (11905)		1.19 0.93-1.53 C1 Day 8/ Day 7	1.25 0.88-1.76 C1 Day 8/ Day 7
					MIFE 300 mg/d C1 Day 8	400 mg Keto single dose	3240 (760)	median 2.1	NC ^a	47357 (17239)	84.9 (46.6)	1.39 1.13-1.70 C2 Day 8/ Day 7	1.28 1.09-1.49 C2 Day 8/ Day 7
					MIFE 600 mg/d C2 Day 7		3818 (703)	median 4.0	NC ^a	54174 (7305)		1.42 1.13-1.78 Day 7 C2/C1	1.48 1.13-1.94 Day 7 C2/C1
					MIFE 600 mg/d C2 Day 8	400 mg Keto single dose	5264 (795)	median 4.0	NC ^a	69112 (9077)	96.2 (45.4)	1.65 1.30-2.08 Day 8 C2/C1	1.52 1.14-2.02 Day 8 C2/C1

MIFE = mifepristone, Keto = ketoconazole

C1 = Cohort 1, C2 = Cohort 2

AUC_t = AUC0-24 hours following Day 7 or Day 8 dose of MIFE

^a AUC_{tot} = AUC_{total}, not computed (NC) for multiple dosing

TABLE 2

Effects of Co-Administration with Ketoconazole on Mifepristone and Metabolites
Test: Day 17 - 600 mg mifepristone OD + 200 mg Ketoconazole BID
Reference: Day 12 – 600 mg mifepristone OD

Analyte	Parameter	N	Ratio%		
			Test/Reference	Lower 90% CI	Upper 90% CI
Mifepristone	C _{max}	13	127.59	116.66	139.54
	AUC ₀₋₂₄	13	138.01	127.12	149.84
RU 42633	C _{max}	13	105.73	95.92	116.54
	AUC ₀₋₂₄	13	102.33	94.31	111.03
RU 42698	C _{max}	13	169.13	156.36	182.94
	AUC ₀₋₂₄	13	166.86	155.06	179.57
RU 42848	C _{max}	13	95.48	90.82	100.38
	AUC ₀₋₂₄	13	94.88	91.33	98.56

Table 3

Effects of Co-Administration with Mifepristone on Ketoconazole
Test: Day 17 - 600 mg mifepristone OD + 200 mg Ketoconazole BID
Reference: Day -1 – 200 mg Ketoconazole Single Dose

Parameter	N	Ratio% Test/Reference	Lower 90% CI	Upper 90% CI
C _{max}	14	252.71	214.85	297.26
AUC	14	365.36	333.78	399.93

Table 4

Cross-study Comparison of Exposure to Mifepristone and Metabolites
Test: Present Study Day 17 - 600 mg mifepristone OD + 200 mg Ketoconazole BID
Reference: Historic Study Day 7 – 1200 mg mifepristone OD alone

Analyte	Parameter	Ratio% Test/Ref	Lower 90% CI	Upper 90% CI
Mifepristone	C _{max}	84.64	72.92	98.23
	AUC ₀₋₂₄	87.27	74.72	101.94
RU 42633	C _{max}	96.31	80.83	114.75
	AUC ₀₋₂₄	91.34	76.95	108.43
RU 42698	C _{max}	116.55	97.47	139.38
	AUC ₀₋₂₄	118.18	97.90	142.66
RU 42848	C _{max}	82.45	70.31	96.70
	AUC ₀₋₂₄	81.43	69.71	95.11

All doses given within 30 minutes after typical (34%) fat meal

Table 5



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Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY. DOCKET NO, TOT CLAIMS, IND CLAIMS. Row 1: 15/627,359, 06/19/2017, 1629, 1340, 085178-1053027-011410US, 30, 4

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Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

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**** SMALL ENTITY ****

Title

CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND
CYP3A INHIBITORS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.



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

Table with 4 columns: APPLICATION NUMBER (15/627,359), FILING OR 371(C) DATE (06/19/2017), FIRST NAMED APPLICANT (Joseph K. Belanoff), ATTY. DOCKET NO./TITLE (085178-1053027-011410US)

CONFIRMATION NO. 2957

FORMALITIES LETTER

144579
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309



Date Mailed: 06/27/2017

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

SUMMARY OF FEES DUE:

The fee(s) required within TWO MONTHS from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ 200 for 41 electronically equivalent pages in excess of 100 application size fee.
• \$(0) previous unapplied payment amount.
• \$ 200 TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".
<https://portal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at <http://www.uspto.gov/ebc>.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/lvongxay/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
15/627,359

APPLICATION AS FILED - PART I

(Column 1) (Column 2)

FOR	NUMBER FILED	NUMBER EXTRA
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A
TOTAL CLAIMS (37 CFR 1.16(j))	30 minus 20 = *	10
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 = *	1
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.

SMALL ENTITY

RATE(\$)	FEE(\$)
N/A	70
N/A	300
N/A	360
x 40 =	400
x 210 =	210
	200
	0.00
TOTAL	1540

OR OTHER THAN SMALL ENTITY

RATE(\$)	FEE(\$)
N/A	
N/A	
N/A	
TOTAL	

APPLICATION AS AMENDED - PART II

(Column 1) (Column 2) (Column 3)

AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total (37 CFR 1.16(i))	*	Minus	**	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=
	Application Size Fee (37 CFR 1.16(s))				
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					

SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

OR OTHER THAN SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

(Column 1) (Column 2) (Column 3)

AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total (37 CFR 1.16(i))	*	Minus	**	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=
	Application Size Fee (37 CFR 1.16(s))				
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

OR OTHER THAN SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** 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 found in the appropriate box in column 1.

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.

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the above-application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
15/627,359	June 19, 2017

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A).

- I hereby appoint Practitioners associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

144579

OR

- I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

- The address associated with the above-mentioned Customer Number.

OR

- The address associated with Customer Number:

OR

<input type="checkbox"/> Firm or Individual name			
Address			
City	State	Zip	
Country			
Telephone	Email		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Concept Therapeutics, Inc.

- Inventor or Joint Inventor (title not required below)
- Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)(provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Date (optional)	
Name	Joseph Belanoff	
Title	CEO	

NOTE: Signature – This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

*Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.

Electronic Acknowledgement Receipt

EFS ID:	29640428
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	28-JUN-2017
Filing Date:	19-JUN-2017
Time Stamp:	17:45:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	7_POA_15627359_1053027_01 1410US_CYP3A_600.pdf	445241 0daffb1c431edcc49a94311bc1bef7c69a2d 2cb4	no	1

Warnings:

Information:	
Total Files Size (in bytes):	445241
<p>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.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a 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.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> 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.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> 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.</p>	

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on August 3, 2017

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION
OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: not yet assigned

Technology Center/Art Unit: 1629

RESPONSE TO NOTICE OF MISSING
PARTS OF NONPROVISIONAL
APPLICATION

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

Commissioner:

In reply to the Notice to File Missing Parts of Nonprovisional Application, dated June 27, 2017, we believe the Notice was issued in error, and that no further fees are due since the application consists of only a total of 98 pages (93 pages Specification; 3 pages Claims; 1 page Abstract; 1 page Drawing).

Applicant requests that the USPTO re-process the application, and proceed with consideration of the TrackOne Request and prioritized examination of this application.

Applicant believes there is no fee required. However, the Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.16, or credit any overpayment to Account No. 20-1430.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Kenneth A. Weber/

Kenneth A. Weber

Registration No. 31,677

Tel: (415) 576-0200

Email: KWeber@KilpatrickTownsend.com

Electronic Acknowledgement Receipt

EFS ID:	29980788
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	03-AUG-2017
Filing Date:	19-JUN-2017
Time Stamp:	18:35:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	respNOMP.pdf	65897 c529d173ba928b5c4cb542c0bfacee3ad69780e	no	1

Warnings:

Information:	
Total Files Size (in bytes):	65897
<p>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.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a 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.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> 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.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> 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.</p>	



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Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY. DOCKET NO, TOT CLAIMS, IND CLAIMS. Row 1: 15/627,359, 06/19/2017, 1629, 1340, 085178-1053027-011410US, 30, 4

CONFIRMATION NO. 2957

FILING RECEIPT

144579
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309



Date Mailed: 08/07/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections

Inventor(s)

Joseph K. Belanoff, Menlo Park, CA;

Applicant(s)

Corcept Therapeutics, Inc., Menlo Park, CA;

Power of Attorney: The patent practitioners associated with Customer Number 144579

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/465,772 03/01/2017
and claims benefit of 62/466,867 03/03/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 06/23/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is US 15/627,359

Projected Publication Date: 11/16/2017

Non-Publication Request: No

Early Publication Request: Yes

**** SMALL ENTITY ****

Title

CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND
CYP3A INHIBITORS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Table with 4 columns: APPLICATION NUMBER (15/627,359), FILING OR 371(C) DATE (06/19/2017), FIRST NAMED APPLICANT (Joseph K. Belanoff), ATTY. DOCKET NO./TITLE (085178-1053027-011410US)

CONFIRMATION NO. 2957

WITHDRAWAL NOTICE



144579
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

Date Mailed: 08/07/2017

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 06/27/2017. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/agizaw/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
15/627,359

APPLICATION AS FILED - PART I

(Column 1) (Column 2)

FOR	NUMBER FILED	NUMBER EXTRA
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A
TOTAL CLAIMS (37 CFR 1.16(j))	30 minus 20 = *	10
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 = *	1
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.

SMALL ENTITY

RATE(\$)	FEE(\$)
N/A	70
N/A	300
N/A	360
x 40 =	400
x 210 =	210
	0.00
	0.00
TOTAL	1340

OR OTHER THAN SMALL ENTITY

RATE(\$)	FEE(\$)
N/A	
N/A	
N/A	
TOTAL	

APPLICATION AS AMENDED - PART II

(Column 1) (Column 2) (Column 3)

AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total (37 CFR 1.16(i))	*	Minus	**	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=
	Application Size Fee (37 CFR 1.16(s))				
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					

SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

OR OTHER THAN SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

(Column 1) (Column 2) (Column 3)

AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total (37 CFR 1.16(i))	*	Minus	**	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=
	Application Size Fee (37 CFR 1.16(s))				
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

OR OTHER THAN SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** 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 found in the appropriate box in column 1.



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US

CONFIRMATION NO. 2957

POA ACCEPTANCE LETTER



144579
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

Date Mailed: 08/07/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/03/2017.

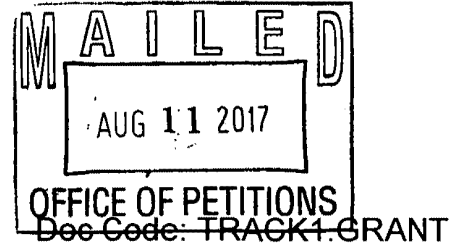
The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/agizaw/



KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
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Suite 2800
Atlanta GA 30309



Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 15/627,359
<p>1. THE REQUEST FILED <u>June 19, 2017</u> IS GRANTED.</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. <input checked="" type="checkbox"/> for an original nonprovisional application (Track I).</p> <p>B. <input type="checkbox"/> for an application undergoing continued examination (RCE).</p> <p>2. The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <u>petition for extension of time</u> to extend the time period for filing a reply;</p> <p>B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims,</u> or a multiple dependent claim;</p> <p>C. filing a <u>request for continued examination;</u></p> <p>D. filing a notice of appeal;</p> <p>E. filing a request for suspension of action;</p> <p>F. mailing of a notice of allowance;</p> <p>G. mailing of a final Office action;</p> <p>H. completion of examination as defined in 37 CFR 41.102; or</p> <p>I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.</p> <p>/Brian W. Brown/ [Signature]</p> <p>Petitions Examiner, Office of Petitions (Title)</p>	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15/627,359	
	Filing Date		June 19, 2017	
	First Named Inventor	Joseph K. Belanoff		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	085178-1053027		

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	B1.	2008060391	WO	A2	22 May 2008	MERCK & CO INC		
	B2.	2009050136	WO	A2	23 Apr 2009	ULMANN et al.		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	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 ⁵
	B3.	ALBERTSON et al., "Effect of the antigluco-corticoid RU486 on adrenal steroidogenic enzyme activity and steroidogenesis," EP J. of Endocrinology. (1994) 130: 195-200	

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	Attorney Docket Number	085178-1053027	

	B4.	ASSER et al., "Autocrine positive regulatory feedback of glucocorticoid secretion: Glucocorticoid receptor directly impacts H295R human adrenocortical cell function," Mol. Cell. Endocrino. (2014) 395(1-2):1-9	
	B5.	BENAGIANO et al., "Selective progesterone receptor modulators 3: use in oncology, endocrinology and psychiatry," Expert Opin Pharmacother October 2008, 9(14):2487-2496	
	B6.	BERTAGNA et al., "Pituitary-Adrenal Response to the Antigluco-corticoid Action of RU 486 in Cushing's Syndrome," J. Clin Endocrinol Metab (1986) 63:639-643	
	B7.	CHROUSOS et al., "Glucocorticoids and glucocorticoid antagonists: Lessons from RU 486," Kidney International, Vol. 34, Suppl. 26 (1988), pp. S-18-S-23	
	B8.	CHU et al., "Successful Long-Term Treatment of Refractory Cushing's Disease with High-Dose Mifepristone (RU 486)," J. Clin Endocrinology Metab, August 2001, 86(8):3568-3573	
	B9.	CUNEO et al., Metyrapone pre-treated inferior petrosal sinus sampling in the differential diagnosis of ACTH-dependent Cushing's syndrome. Clin Endocrinol (Oxf). 1997 May;46(5):607-18	
	B10.	EHRENKRANZ et al. "SUN-66: Using Mifepristone to Differentiate Cushing's Disease from Cushing's Syndrome," The Endocrine Society's 95 th Annual Meeting and Expo, June 15-18, 2013 (San Francisco) Abstract	

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	Art Unit		1629
	Examiner Name		
	Attorney Docket Number		085178-1053027

	B11.	EL-SHAFIE, et al., “Adrenocorticotrophic Hormone-Dependent Cushing's Syndrome: Use of an octreotide trial to distinguish between pituitary or ectopic sources,” Sultan Qaboos University Medical Journal, Vol.15, Issue 1, pp. 120-123 (Epub. 21 January 2015)	
	B12.	FEIN, et al., “Sustained weight loss in patients treated with mifepristone for Cushing’s syndrome: a follow-up analysis of the SEISMIC study and long-term extension. BMC Endocr Disord. 15:63 (2015)	
	B13.	GROSS et al., “Mifepristone Reduces Weight Gain and Improves Metabolic Abnormalities Associated With Risperidone Treatment in Normal Men.” Obesity Vol. 18 No. 12/December 2010; Published online 25 March 2010	
	B14.	HEALY et al., “Pituitary and adrenal responses to the anti-progesterone and anti-gluocorticoid steroid RU486 in primates,” J. Clin Endocrinol Metab (1983) 57(4):863-865	
	B15.	LEE et al., “Office of Clinical Pharmacology Review NDA 20687 (Addendum, Korlym™, Mifepristone) (2012)	
	B16.	LELY VAN DER A-J et al., “Rapid Reversal of Acute Psychosis in the Cushing Syndrome with the Cortisol-Receptor Antagonist Mifepristone (RU 486),” Annals of Internal Medicine, 15 January 1991, 114(2):143-144	
	B17.	Medical Encyclopedia of Medline (http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm) 4 pages, October 2005	

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	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	085178-1053027	

	B18.	MONCET et al. “Ketoconazole therapy: an efficacious alternative to achieve eucortisolism in patients with Cushing’s syndrome. <i>Medicina</i> 67:26-31 (2007)	
	B19.	REIMONDO et al., “The corticotrophin-releasing hormone test is the most reliable noninvasive method to differentiate pituitary from ectopic ACTH secretion in Cushing’s syndrome,” <i>Clinical Endocrinology</i> , (2003) 58:718-724	
	B20.	RITZEL et al.. “ACTH after 15 min distinguishes between Cushing's disease and ectopic Cushing's syndrome: a proposal for a short and simple CRH test,” <i>Europe an Journal of Endocrinology</i> , Vol.173, No.2, pp.197-204 (2015)	
	B21.	SARKAR, “Mifepristone: bioavailability, pharmacokinetics and use-effectiveness,” <u><i>European Journal of Obstetrics and Gynecology and Reproductive Biology</i></u> , Vol. 101, pp.113-120 (2002)	
	B22.	TSIGOS, “Differential Diagnosis and Management of Cushing’s Syndrome”, <i>Ann. Rev. Med.</i> Vol. 47, pp 443-461 (1996)	
	B23.	PCT/US2017/013974, International Search Report and Written Opinion, January 18, 2017, pp. 1-12	
	B24.	PCT/EP2008/063699, International Search Report, May 6, 2009, pp. 2-6	

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	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	085178-1053027	

	B25.	FDA Label for KORLYM [®] dated October 2016	
	B26.	15/627,368, "Non-Final Office Action", August 8, 2017, 13 pages	

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			
<p>¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.</p>			

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 May 2008 (22.05.2008)

PCT

(10) International Publication Number
WO 2008/060391 A2

- (51) International Patent Classification: **Not classified**
- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) International Application Number: PCT/US2007/022449
- (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (22) International Filing Date: 23 October 2007 (23.10.2007)
- (84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (25) Filing Language: English
- (30) Priority Data:

60/853,655	23 October 2006 (23.10.2006)	US
60/923,337	13 April 2007 (13.04.2007)	US
- (26) Publication Language: English
- (71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **BUNGARD, Christopher, J.** [NZ/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MANIKOWSKI, Jesse, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **PERKINS, James, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MEISSNER, Robert** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- Published:**
— *without international search report and to be republished upon receipt of that report*



WO 2008/060391 A2

(54) Title: 2-[1-PHENYL-5-HYDROXY OR METHOXY-4ALPHA-METHYL-HEXAHYDROCYCLOPENTA [F]INDAZOL-5-YL]ETHYL PHENYL DERIVATIVES AS GLUCOCORTICOID RECEPTOR LIGANDS

(57) Abstract: The present invention is directed to 2-[1-phenyl-5-hydroxy-4alpha-methyl- hexahydrocyclopenta[f]indazol-5-yl]ethyl phenyl derivatives as glucocorticoid receptor ligands useful for treating a variety of autoimmune and inflammatory diseases or conditions. Pharmaceutical compositions and methods of use are also included.

TITLE OF THE INVENTION

2-[1-PHENYL-5-HYDROXY-4ALPHA-METHYL-HEXAHYDROCYCLOPENTA
[J]INDAZOL-5-YL]ETHYL PHENYL DERIVATIVES AS GLUCOCORTICOID RECEPTOR
LIGANDS

5

BACKGROUND OF THE INVENTION

Intracellular receptors (IR's) are a class of structurally related proteins involved in the regulation of gene expression. The steroid hormone receptors are a subset of this superfamily whose natural ligands are typically comprised of endogenous steroids such as estradiol, progesterone, and cortisol. Man-made ligands to these receptors play an important role in human health and, of these receptors, the glucocorticoid receptor has an essential role in regulating human physiology and immune response. Steroids that interact with the glucocorticoid receptor have been shown to be potent anti-inflammatory agents, although cross-reactivity with other steroid hormone receptors such as the mineralocorticoid, progesterone and androgen receptors can lead to problematic ancillary pharmacology.

The dissociation of transactivation from transrepression at the glucocorticoid receptor is believed to be an approach toward improving the side-effect profile related to steroid therapy. The beneficial anti-inflammatory activity of GR modulators, such as steroids, is believed to occur through the transrepression of genes encoding for proinflammatory cytokines, adhesion molecules and enzymes. Many of the undesirable side-effects associated with such agents are believed to occur through the transactivation, or induction, of gene transcription leading to the downstream perturbation of homeostatic endocrine function. Some of these affected metabolic processes include induced gluconeogenesis, induced amino acid degradation, osteoporosis, suppression of HPA axis, induction of secondary adrenal suppression, changes in electrolyte concentration, changes in lipid metabolism, growth retardation, impaired wound healing and skin thinning. Weak, partial and full agonism of GR related to transrepression and transactivation, including potential antagonism of the receptor regarding transactivation, may be applied to the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis and asthma. For recent reviews see: (a) *Recent Advances in Glucocorticoid Receptor Action*; Cato, A.C.B., Schacke, H., Asadullah, K., Eds.; Springer-Verlag: Berlin-Heidelberg, Germany, 2002. (b) Coghlan, M.J.; Elmore, S.W.; Kym, P.R.; Kort, M.E. In *Annual Reports in Medicinal Chemistry*; Doherty, A.M., Hagmann, W.K., Eds.; Academic Press: San Diego, CA, USA, 2002; Vol. 37, Ch. 17, pp 167-176.

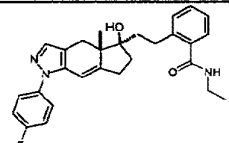
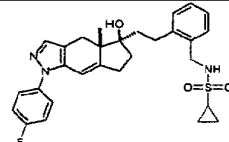
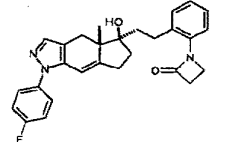
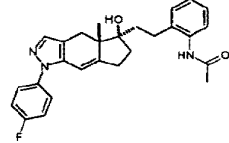
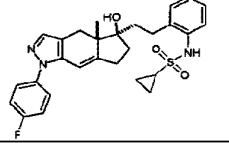
Glucocorticoid receptor modulators are described in WO 2003/061651, WO2003/086294, WO2004/026248, WO2004/075840 and WO2004093805. An object of the invention is the discovery of novel compounds that modulate the glucocorticoid receptor. Another object of the invention is the discovery of novel glucocorticoid receptor modulators with superior transactivation and transrepression activity profiles. It is believed that such compounds would have potent anti-inflammatory and immunosuppressive activity and possess advantages over current steroid therapies with respect to side effects, efficacy, toxicity and/or metabolism.

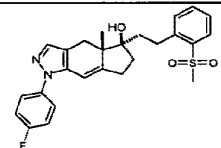
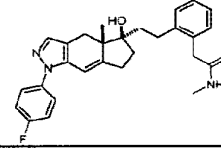
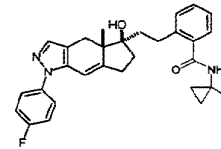
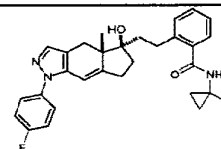
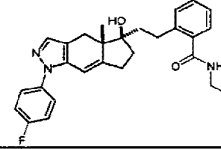
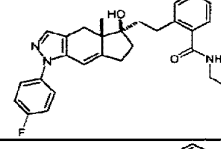
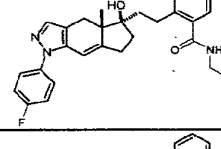
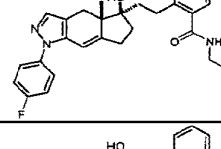
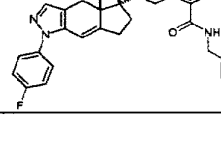
SUMMARY OF THE INVENTION

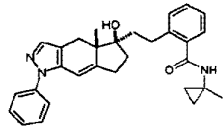
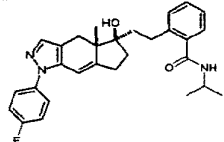
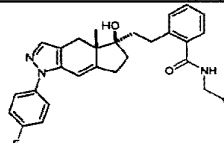
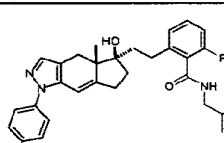
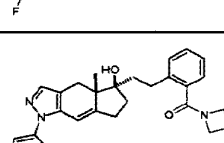
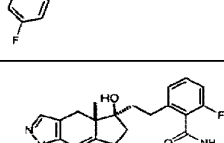
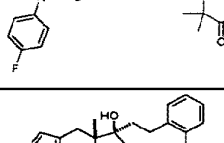
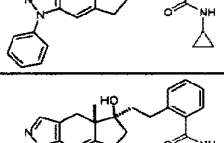
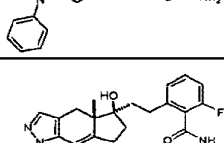
The present invention is directed to 2-[1-phenyl-5-hydroxy-4 α -methyl-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl phenyl derivatives as glucocorticoid receptor ligands useful for treating a variety of autoimmune and inflammatory diseases or conditions. Pharmaceutical compositions and methods of use are also included.

DETAILED DESCRIPTION OF THE INVENTION

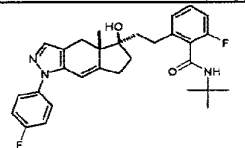
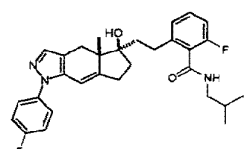
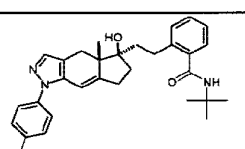
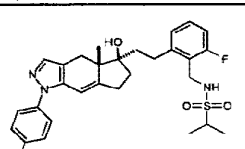
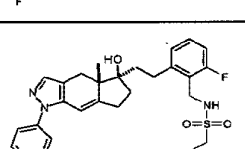
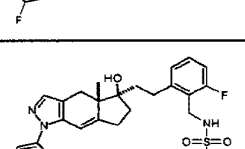
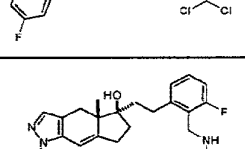
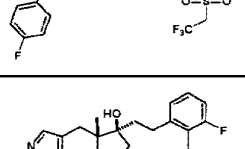
The invention encompasses a compound selected from the following group:

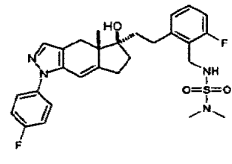
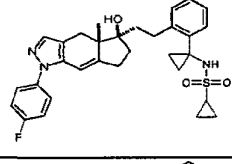
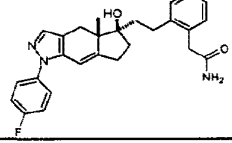
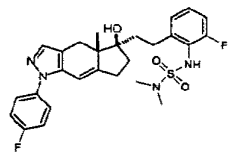
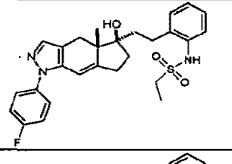
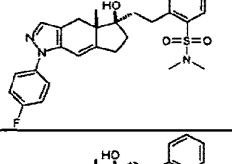
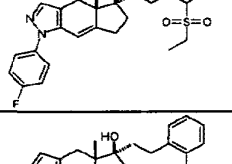
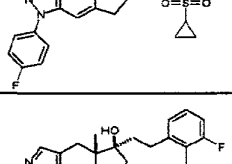
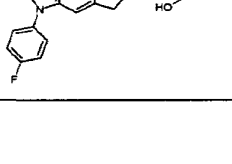
Ex.	STRUCTURE	NAME	M+1
2		<i>N</i> -ethyl-2-{2-[(4 α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[<i>f</i>]indazol-5-yl]ethyl}benzamide	460.2395
5		<i>N</i> -(2-{2-[(4 α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[<i>f</i>]indazol-5-yl]ethyl}benzyl)cyclopropanesulfonamide	522.2230
11		1-(2-{2-[(4 α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[<i>f</i>]indazol-5-yl]ethyl}phenyl)azetidin-2-one	458.2238
14		<i>N</i> -(2-{2-[(4 α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[<i>f</i>]indazol-5-yl]ethyl}phenyl)acetamide	446.2239
15		<i>N</i> -(2-{2-[(4 α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[<i>f</i>]indazol-5-yl]ethyl}phenyl)cyclopropanesulfonamide	508.2055

Ex.	STRUCTURE	NAME	M+1
19		(4 α S,5R)-1-(4-fluorophenyl)-4 α -methyl-5-{2-[2-(methylsulfonyl)phenyl]ethyl}-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	467.1793
23		2-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)-N-methylacetamide	460.2395
26		methyl 1-[(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoyl)amino]cyclopropanecarboxylate	530.2450
28		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-(1-methylcyclopropyl)benzamide	486.2548
29		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-isobutylbenzamide	488.2720
30		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-propylbenzamide	474.2564
31		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-(3,3,3-trifluoro-2-methylpropyl)benzamide	542.2443
32		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-(2-methylprop-2-en-1-yl)benzamide	486.2562
33		N-allyl-2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	472.2404

Ex.	STRUCTURE	NAME	M+1
34		2-{2-[(4αS,5R)-5-hydroxy-4α-methyl-1-phenyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-(1-methylcyclopropyl)benzamide	468.2630
35		2-{2-[(4αS,5R)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-isopropylbenzamide	474.2565
37		N-(cyclopropylmethyl)-2-{2-[(4αS,5R)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	486.2588
38		2-fluoro-6-{2-[(4αS,5R)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-(3,3,3-trifluoro-2-methylpropyl)benzamide	560.2323
40		(4αS,5R)-5-{2-[2-(azetidin-1-ylcarbonyl)phenyl]ethyl}-1-(4-fluorophenyl)-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	472.2387
41		methyl N-(2-fluoro-6-{2-[(4αS,5R)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoyl)-2-methylalaninate	550.2513
42		N-cyclopropyl-2-{2-[(4αS,5R)-5-hydroxy-4α-methyl-1-phenyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	454.2504
43		2-{2-[(4αS,5R)-5-hydroxy-4α-methyl-1-phenyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	414.2188
44		2-fluoro-6-{2-[(4αS,5R)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-(2-methylprop-2-en-1-yl)benzamide	504.2456

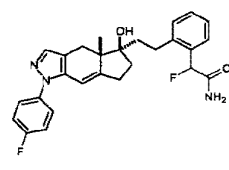
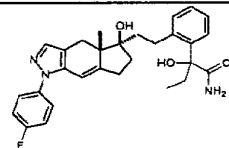
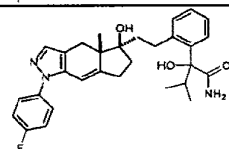
Ex.	STRUCTURE	NAME	M+1
45		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-[(2R)-3,3,3-trifluoro-2-methylpropyl]benzamide	542.2414
46		(4 α S,5R)-1-(4-fluorophenyl)-4 α -methyl-5-{2-[2-(piperidin-1-ylcarbonyl)phenyl]ethyl}-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	500.2696
47		(4 α S,5R)-1-(4-fluorophenyl)-4 α -methyl-5-{2-[2-(pyrrolidin-1-ylcarbonyl)phenyl]ethyl}-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	486.2538
48		N-[(1R)-1,2-dimethylpropyl]-2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	520.2765
49		2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-propylbenzamide	492.2456
51		2-{2-[(4 α S,5R)-1-(3,4-difluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-ethylbenzamide	478.2302
52		methyl N-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoyl)-2-methylalaninate	532.2594
55		N-(2,2-dimethylpropyl)-2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	520.2768
57		N-allyl-2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	490.2302

Ex.	STRUCTURE	NAME	M+1
59		<i>N</i> -(<i>tert</i> -butyl)-2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	506.2610
61		2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}- <i>N</i> -isobutylbenzamide	506.2615
62		<i>N</i> -(<i>tert</i> -butyl)-2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	488.2701
83		<i>N</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzyl)propane-2-sulfonamide	542.2313
84		<i>N</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzyl)ethanesulfonamide	528.2124
85		1,1-dichloro- <i>N</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzyl)methanesulfonamide	582.1204
86		2,2,2-trifluoro- <i>N</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzyl)ethanesulfonamide	582.1741
88		<i>N</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzyl)cyclopropanesulfonamide	540.2124

Ex.	STRUCTURE	NAME	M+1
89		<i>N'</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzyl)- <i>N,N</i> -dimethylsulfamide	543.2265
91		<i>N</i> -[1-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)cyclopropyl]cyclopropanesulfonamide	548.2371
107		2-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)acetamide	446.2236
113		<i>N'</i> -(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)- <i>N,N</i> -dimethylsulfamide	529.2068
114		<i>N</i> -(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)ethanesulfonamide	496.2055
138		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}- <i>N,N</i> -dimethylbenzenesulfonamide	496.2062
143		(4 α S,5R)-5-{2-[2-(ethylsulfonyl)phenyl]ethyl}-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	481.1964
144		(4 α S,5R)-5-{2-[2-(cyclopropylsulfonyl)phenyl]ethyl}-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	444.1717
148		(4 α S,5R)-5-{2-[3-fluoro-2-(hydroxymethyl)phenyl]ethyl}-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	437.2026

Ex.	STRUCTURE	NAME	M+1
150		2-(2-((4α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)ethyl)phenyl)-2-hydroxypropanamide	476.2361
151		(4α <i>S</i> ,5 <i>R</i>)-5-(2-(2-((1 <i>S</i>)-1-amino-2,2,2-trifluoroethyl)-3-fluorophenyl)ethyl)-1-(4-fluorophenyl)-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	504.2060
152		(4α <i>S</i> ,5 <i>R</i>)-5-(2-(2-((1 <i>R</i>)-1-amino-2,2,2-trifluoroethyl)-3-fluorophenyl)ethyl)-1-(4-fluorophenyl)-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-ol	504.2059
156		1-(2-(2-((4α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)ethyl)benzoyl)azetidin-3-one	486.2162
157		1-(2-(2-((4α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)ethyl)phenyl)acetone	445.2285
159		5-fluoro-2-(2-((4α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)ethyl)benzamide	450.1998
160		2-((<i>E</i>)-2-((4α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)vinyl)benzenesulfonamide	466.1593
163		5-fluoro-2-(2-((4α <i>S</i> ,5 <i>R</i>)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)ethyl)benzonitrile	432.1886
168		2-(2-((4α <i>S</i> ,5 <i>R</i>)-1-(3,4-difluorophenyl)-5-hydroxy-4α-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl)ethyl)-6-fluorobenzamide	468.1889

Ex.	STRUCTURE	NAME	M+1
170		5-chloro-2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	466.1693
172		2-{2-[(4 α S,5R)-1-(3,4-difluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide	450.1992
174		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-4-methylbenzamide	446.2242
185		2-{2-[(4 α S,5R)-1-(4-chlorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-6-fluorobenzamide	466.1721
189		2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-6-methoxybenzamide	462.2182
191		2-{2-[(4 α S,5R)-1-(3-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-6-methylbenzamide	446.2223
194		2-(2-fluoro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)acetamide	464.2150
196		2-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)propanamide	460.2373
197		2-(2-chloro-6-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)acetamide	480.1823

Ex.	STRUCTURE	NAME	M+1
198		2-fluoro-2-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)acetamide	464.2122
199		2-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)-2-hydroxybutanamide	490.2472
201		2-(2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)-2-hydroxy-3-methylbutanamide	504.2631

or a pharmaceutically acceptable salt of any of the foregoing compounds.

The above examples were prepared following the general synthetic scheme and procedures described below.

5 Another embodiment of the invention encompasses a pharmaceutical composition comprising a compound selected from the above table in combination with a pharmaceutically acceptable carrier.

10 Another embodiment of the invention encompasses a method for treating a glucocorticoid receptor mediated disease or condition in a mammalian patient in need of such treatment comprising administering the patient a compound selected from the above table in an amount that is effective for treating the glucocorticoid receptor mediated disease or condition.

15 Within this embodiment is encompassed the above method wherein the glucocorticoid receptor mediated disease or condition is selected from the group consisting of: tissue rejection, leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's
20 syndrome, obesity, metabolic syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyarthritis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic

edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic
5 lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer,
10 Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

Another embodiment of the invention encompasses a method of selectively modulating the activation, repression, agonism and antagonism effects of the glucocorticoid
15 receptor in a mammal comprising administering to the mammal a compound selected from the above table in an amount that is effective to modulate the glucocorticoid receptor.

Abbreviations

The following abbreviations have the indicated meanings:

	AIBN	=	2,2'-azobisisobutyronitrile
	B.P.	=	benzoyl peroxide
5	Bn	=	benzyl
	CCl ₄	=	carbon tetrachloride
	D	=	-O(CH ₂) ₃ O-
	DAST	=	diethylamine sulfur trifluoride
	DCC	=	dicyclohexyl carbodiimide
10	DCI	=	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide
	DEAD	=	diethyl azodicarboxylate
	DIBAL	=	diisobutyl aluminum hydride
	DME	=	ethylene glycol dimethylether
15	DMAP	=	4-(dimethylamino)pyridine
	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethyl sulfoxide
	Et ₃ N	=	triethylamine
	LDA	=	lithium diisopropylamide
20	m-CPBA	=	metachloroperbenzoic acid
	NBS	=	N-bromosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
25	Ph	=	phenyl
	1,2-Ph	=	1,2-benzenediyl
	Pyr	=	pyridinediyl
	Qn	=	7-chloroquinolin-2-yl
	Rs	=	-CH ₂ SCH ₂ CH ₂ Ph
30	r.t.	=	room temperature
	rac.	=	racemic
	THF	=	tetrahydrofuran
	THP	=	tetrahydropyran-2-yl

Alkyl group abbreviations

	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
5	i-Pr	=	isopropyl
	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
10	c-Pr	=	cyclopropyl
	c-Bu	=	cyclobutyl
	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

15 Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of the invention contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of the invention.

20 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are
25 encompassed with compounds of the invention.

Compounds of the invention may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example MeOH or EtOAc or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically
30 active amine as a resolving agent or on a chiral HPLC column.

Alternatively, any enantiomer of a compound of the invention may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Dose Ranges

It will be understood that, as used herein, references to the compounds of the invention are meant to also include the pharmaceutically acceptable salts.

The magnitude of prophylactic or therapeutic dose of a compound of the invention will, of course, vary with the nature and the severity of the condition to be treated and with the particular compound of the present invention and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from about 0.5 mg to about 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain from about 1 mg to about 2 g of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

10 Pharmaceutical Compositions

For the treatment of glucocorticoid receptor mediated diseases the compounds of the invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, solutions, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be

employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis

oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example
5 polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in
10 the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and
15 solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

20 The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

25 For topical use, creams, ointments, gels, solutions or suspensions, etc., containing a compound of the invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

30 For compounds of the invention with poor solubility, the following formulation technologies may be adopted: conventional solid with a surfactant/polymer, solid dispersion (spray dried or hot melt extrusion), liquid filled capsules or nanomilled formulation. Such technologies are known in the art.

Utilities

The ability of the compounds of the invention to modulate glucocorticoid receptors makes them useful for treating, preventing or reversing the progression of a variety of inflammatory and autoimmune diseases and conditions. Thus, the compounds of the present

5 invention are useful to treat, prevent or ameliorate the following diseases or conditions:
inflammation, tissue rejection, auto-immunity, various malianancies, such as leukemias and
lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia,
rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell
lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia,
10 stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic
primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia,
cerebral edema, thrombocytopenia, Little's syndrome, hypertension, cardiac arrhythmias, obesity
and metabolic syndrome.

The compounds of the present invention are also useful for treating, preventing or
15 reversing the progression of disease states involving systemic inflammation such as
inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's
granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay
fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease,
asthma, tendonitis, bursitis, Crohn's disease, stress and urge related urinary incontinence, age
20 related sarcopenia, ulcerative colitis, autoimmune chronic active hepatitis, rejection of
transplanted organ, prevention of organ transplant rejection, hepatitis, and cirrhosis.

The compounds of the present invention are useful for treating, preventing or
reversing the progression of a variety of topical diseases such as inflammatory scalp alopecia,
panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma
25 gangrenosum, pemphigus vulgaris, buflous pernphigoid, systemic lupus erythematosus,
dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis,
inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary
hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis,
erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous
30 T-cell lymphoma, neoplasm, HPA axis dysregulation in psychiatric disease, schizophrenia,
bipolar disorder, psychotic major depression, posttraumatic syndrom,

The compounds of the present invention are also useful in treating, preventing or
reversing the progression of disease states associated with Human Immunodeficiency Virus
(HIV), cell apoptosis, and cancer including, but not limited to, Kaposi's sarcoma, immune system

activation and modulation, desensitization of inflammatory responses, IIL- 1 expression, natural killer cell development, lymphocytic leukemia, and treatment of retinitis pigmentosa. Cognitive and behavioral processes are also susceptible to glucocorticoid therapy where antagonists would potentially be useful in the treatment of processes such as cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, prevention of cluster headache, schizophrenia, stroke, sleep disorders, and anxiety.

The compounds of the invention are also useful for treating sarcoidosis, disease with enlarged lymph tissue, spleen and liver, follicular b-cell lymphoma, chronic malignant t-cell lymphoma of the skin, a group of lymphomas of the skin, non-hodgkin's lymphoma, diffuse large b-cell lymphoma, type of leukemia - acute lymphocytic leukemia, type of leukemia - chronic lymphocytic leukemia, increased calcium in the blood from cancer, thyroid gland inflammation, condition caused by excess secretion of male hormones, addison's disease, asthma, worsening of asthma decreased function of the adrenal gland, inflammation of the joints due to gout, disease in which body has immune response against itself, destruction of red blood cells by body's own antibodies, infiltration of white blood cells into the lungs, crohn's disease, inflammatory bowel disease a hereditary progressive anemia of unknown cause, anemia from too few young red blood cells, low platelet count and bleeding of unknown cause, decreased platelets due to a disease state or a drug, multiple sclerosis, inflammation of the heart with rheumatic fever, inflammation of the nose due to an allergy, vocal cord swelling, beryllium poisoning, nephrotic syndrome, atopic dermatitis, contact dermatitis, chronic inflammatory skin disease marked by blisters, blistering skin diseases, erythema multiforme, skin rash with sloughing, psoriasis associated with arthritis, psoriasis, skin condition, systemic lupus erythematosus, diffuse proliferative lupus nephritis-a kidney disease, inflammation of skin and muscles all over the body, rheumatoid arthritis, joint inflammatory disease in children and young adults, rheumatic disease causing pain & stiffness in backbone, inflammation of the elbow and surrounding tissue, muscle or bone disorder, giant hives, allergic reaction caused by a drug, body's rejection of a transplanted organ, prevention of transplant rejection, allergic reaction causing serum sickness, disease causing arthritis & urethral & eyelid inflammation, increased calcium in the blood from sarcoidosis, breast cancer that has spread to another part of the body, multiple myeloma, pure red cell aplasia associated with chronic lymphocytic leukemia, a tumor formed of blood vessels, breast cancer, cancer of the prostate gland, joint disease which may include attacks of acute arthritis, brief muscle spasms in an infant, cluster headache prevention, paralysis of one side of the face, myasthenia gravis, rheumatic fever, inflammation of the covering of the heart or pericardium, inflammation of the heart, periarteritis nodosa, inflammation of the artery in the temple area,

5 vasculitis, presence of polyps in the nose, obstructive pulmonary disease, canker sore, failure of small intestines to digest and absorb food, group of skin disorders that resemble blisters, muscle pain and stiffness in shoulder, neck and pelvis, inflammation of several cartilages of the body, fever due to cancer, prevention of cardiac transplant rejection, and prevention of lung transplant rejection.

Preferably, the compounds of the invention are useful for treating the diseases or conditions set for the below.

1. Allergic States

10 Control of severe or incapacitating allergic conditions not responsive to adequate trials of conventional treatment; seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; and drug hypersensitivity reactions.

2. Rheumatic Disorders

15 As adjunctive therapy for short-term administration during an acute episode or exacerbation of: psoriatic arthritis; rheumatoid arthritis including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; post-traumatic osteoarthritis; synovitis of osteoarthritis; and epicondylitis

3. Dermatologic Diseases

20 Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis; and severe seborrheic dermatitis.

4. Ophthalmic Diseases

25 Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis; keratitis; allergic corneal marginal ulcers; herpes zoster ophthalmicus; iritis and iridocyclitis; chorioretinitis; anterior segment inflammation; diffuse posterior uveitis and choroiditis; optic neuritis; and sympathetic ophthalmia.

5. Endocrine Disorders

30 Primary or secondary adrenocortical insufficiency; congenital adrenal hyperplasia; nonsuppurative thyroiditis; and hypercalcemia associated with cancer.

6. Respiratory Diseases

Symptomatic sarcoidosis; Löffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when concurrently accompanied by appropriate antituberculous chemotherapy; and aspiration pneumonitis.

7. Hematologic Disorders

Idiopathic thrombocytopenic purpura in adults; secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia; erythroblastopenia (RBC anemia); and congenital (erythroid) hypoplastic anemia.

5 8. Neoplastic Diseases

For palliative management of: leukemias and lymphomas in adults; and acute leukemia of childhood.

For the treatment of diverse neoplastic diseases such as brain cancer, bone cancer, basal cell carcinoma, adenocarcinoma, lip cancer, mouth cancer, esophageal cancer, small bowel
10 cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, head and neck cancer, skin cancer, prostate cancer, gall bladder cancer, thyroid cancer and renal cell carcinoma.

9. Edematous States

To induce a diuresis or remission of proteinuria in the nephrotic syndrome
15 without uremia, of the idiopathic type or that due to lupus erythematosus. Compounds of the invention may be used to treat patients with cerebral edema from various causes. It may be used also in the preoperative preparation of patients with increased intracranial pressure secondary to brain tumors, and also for palliation of patients with inoperable or recurrent brain neoplasms, and in the management of cerebral edema associated with neurosurgery. Some patients with cerebral
20 edema due to head injury or pseudotumor cerebri also may benefit from therapy with compounds of the invention.

10. Gastrointestinal Diseases

During a critical period of the disease in: ulcerative colitis and regional enteritis.

11. Miscellaneous

25 Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy; Trichinosis with neurologic or myocardial involvement; During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus and acute rheumatic carditis; in combination
30 with ondansetron for the management of nausea and vomiting associated with cisplatin and non-cisplatin emetogenic chemotherapy.

The compounds of the invention are also useful for treating or preventing hypertension, vascular inflammation, urinary incontinence and multiple sclerosis.

12. CNS diseases

For the treatment of HPA axis dysregulation in psychiatric disease, schizophrenia, bipolar disorder, psychotic major depression and posttraumatic syndrome.

5 Combination Therapy

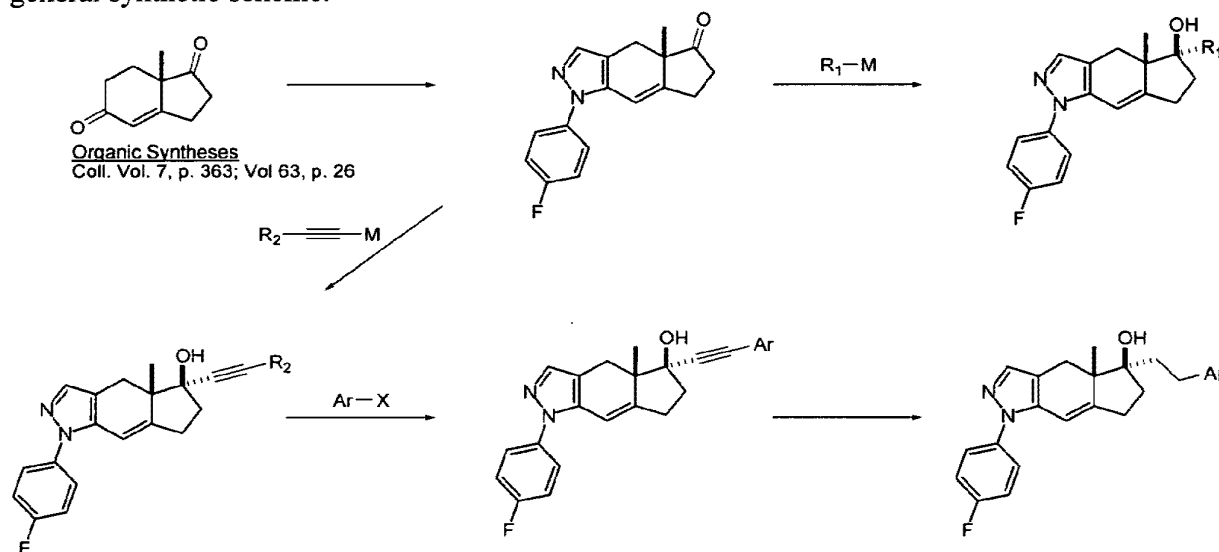
The invention also encompasses a method for treating a glucocorticoid receptor mediated disease comprising concomitantly administering to a patient in need of such treatment a compound of the invention and one or additional more agents. For treating or preventing asthma or chronic obstructive pulmonary disease, the compounds of the invention may be combined with
10 one or more agents selected from the group consisting of: β -agonists (e.g., salmeterol), theophylline, anticholinergics (e.g., atropine and ipratropium bromide), cromolyn, nedocromil and leukotriene modifiers (e.g., montelukast). For treating or preventing inflammation, the compounds of the invention may be combined with one or the following: a salicylate, including acetylsalicylic acid, a non-steroidal antiinflammatory drug, including indomethacin, sulindac,
15 mefenamic, meclofenamic, tolfenamic, tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen and oxaprozin, a TNF inhibitor, including etanercept and infliximab, an IL-1 receptor antagonist, a cytotoxic or immunosuppressive drug, including methotrexate, leflunomide, azathioprine and cyclosporine, a gold compound, hydroxychloroquine or sulfasalazine, penicillamine, darbufelone, and a p38 kinase inhibitor. The compounds of the
20 invention may also be used in combination with bisphosphonates such as alendronate, SERMs (selective estrogen receptor modulators) or cathepsin K inhibitors to treat a glucocorticoid mediated disease and simultaneously causes osteopenia or osteoporosis. The compounds of the invention may also be used in combination with bone anabolic agents such as PTH, Androgens, SARMs (selective androgen receptor modulators), to treat a glucocorticoid mediated disease
25 and simultaneously induces bone loss as exhibited by osteopenia or osteoporosis.

The compounds of the invention may also be used in combination with drugs used to treat age-related sarcopenia or cachexia to treat a glucocorticoid mediated diseases and simultaneously inhibit muscle loss, sarcopenia and frailty.

30

Methods of Synthesis and Examples

Compounds of the invention can be synthesized by following the following general synthetic scheme.



- 5 The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:
- (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C,
 - (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C.,
 - 10 (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;
 - (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism
 - 15 may result in isolation of materials with different melting points in some preparations;
 - (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;
 - (vi) yields are given for illustration only;
 - 20 (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 500 MHz or 600 MHz using the indicated solvent; conventional

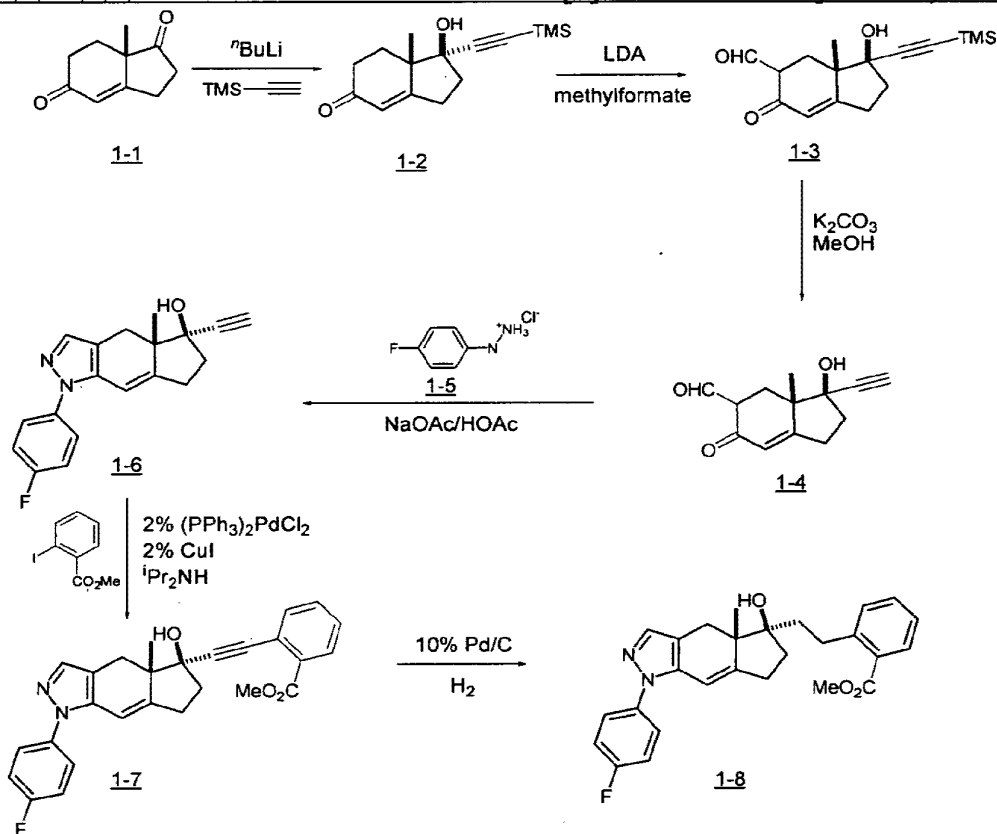
abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1

SYNTHESIS OF 2-{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-YL]ETHYL}BENZOIC ACID

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(1S,7 α S)-1-Hydroxy-7 α -methyl-1-[(trimethylsilyl)ethynyl]-1,2,3,6,7,7 α -hexahydro-5H-inden-5-one (1-2)

A 2.5M solution of ⁿBuLi (27.4 mL, 68.5 mmol) in hexanes was added dropwise to a solution of trimethylsilylacetylene (9.48 mL, 68.5 mmol) in THF (90 mL) at -78 °C. The resulting solution was stirred at -78 °C for 30 min, then a solution of Hajos-Parrish Ketone (*See Organic Syntheses*, Coll. Vol. 7, p.363; Vol 63, p.26) (1-1, 7.5 g, 45.7 mmol) in THF (90 mL) was added and the resulting solution stirred at -78 °C for 30 min. The reaction was quenched with saturated aqueous KH₂PO₄ and the crude product extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-55% EtOAc in hexanes afforded 9.54 g, 80% of 1-2 as a white solid.

MS (ESI): *m/z* = 263.25 (MH⁺).

(3S,3 α S)-3-Hydroxy-3 α -methyl-6-oxo-3-[(trimethylsilyl)ethynyl]-2,3,3 α ,4,5,6-hexahydro-1H-indene-5-carbaldehyde (1-3)

A 1.5 M solution of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (121 mL, 182 mmol) was added to a solution of 1-2 (9.54 g, 36.4 mmol) in THF (400 mL) at -78 °C and the resulting solution stirred at this temperature for 1 hour to afford a thick suspension. Methyl formate (22.6 mL, 364 mmol) was added dropwise over about 15 min and the resulting suspension stirred at -78 °C for 5 hours. The reaction was quenched at -78 °C with 1 M aqueous HCl solution and the aqueous layer checked to ensure it was acidic. The crude product was extracted with EtOAc (x3) and the combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo* to afford crude 1-3 (78% pure) that was used directly in the next step without purification.

MS (ESI): *m/z* = 291.18 (MH⁺).

(3R,3 α S)-3-Ethynyl-3-hydroxy-3 α -methyl-6-oxo-2,3,3 α ,4,5,6-hexahydro-1H-indene-5-carbaldehyde (1-5)

K₂CO₃ (5.03g, 72.8 mmol) was added to a solution of crude 1-4 in MeOH (300 mL) and the resulting suspension stirred at ambient temperature for 90 min. The MeOH was removed *in vacuo* and 1M aqueous HCl was added to the residue and the crude product extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 0-70% EtOAc in hexanes afforded 5.94 g, 75% of 1-6 as a tan solid.

MS (ESI): *m/z* = 219.25 (MH⁺).

(4 α S,5R)-5-Ethynyl-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (1-6)

NaOAc (41.3 g, 504 mmol) was added to a solution of 1-5 (100 g, 458 mmol) and 4-fluorophenylhydrazine hydrochloride (1-5) (82 g, 504 mmol) in acetic acid (916 mL) and the resulting suspension stirred at ambient temperature for 1 hour. The reaction was quenched slowly (caution CO₂ evolution) with saturated aqueous NaHCO₃ solution and the crude product extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Purification by flash chromatography on 1.5 Kg of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 133 g, 94% of 1-6 as a tan solid.
MS (ESI): $m/z = 309.2$ (MH⁺).

Methyl 2-{[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethynyl}benzoate (1-7)

Disopropylamine (2.85 mL, 20.0 mmol) was added to a solution of 1-6 (6.16 g, 20.0 mmol), methyl 2-iodobenzoate (6.28 g, 24.0 mmol), bis(triphenylphosphine)palladium (II) chloride (280 mg, 0.400 mmol), and CuI (76.0 mg, 0.400 mmol) in anhydrous THF (73 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 3.5 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 0-90% EtOAc in hexanes afforded 8.47 g, 96 % of 1-7 as an off white foamy solid.
MS (ESI): $m/z = 443.2$ (MH⁺).

Methyl 2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoate (1-8)

10 % Pd/C (8.16 g) was added to a solution of 1-7 (8.48 g, 19.2 mmol) in EtOAc (128 mL) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 45 min, filtered through a pad of celite and the solvent removed *in vacuo* to afford 7.92 g, 93 % of 1-8 as a pale yellow solid.
MS (ESI): $m/z = 447.2$ (MH⁺).

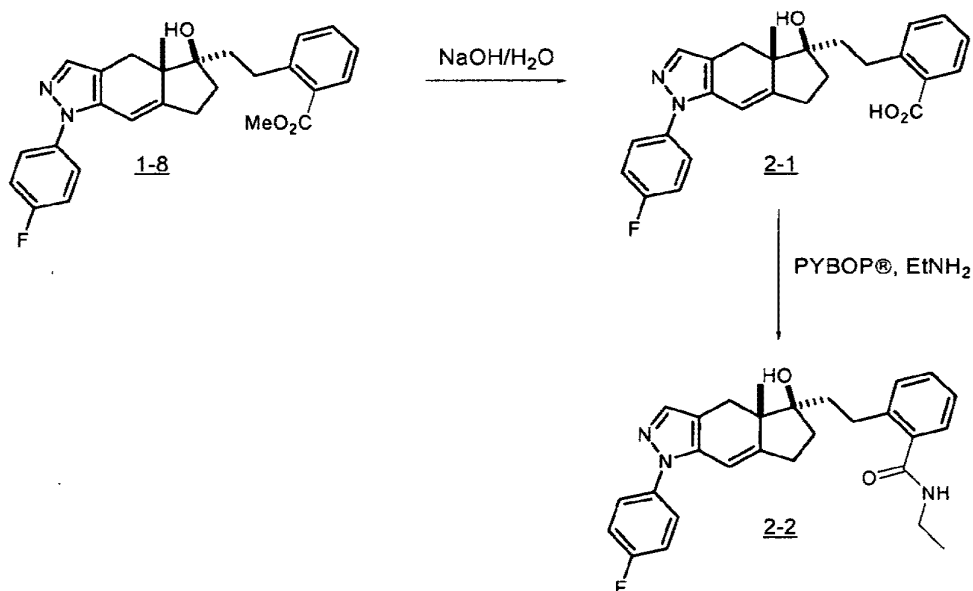
EXAMPLE 2

SYNTHESIS OF 2-{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-YL]ETHYL}-N-ETHYLBENZAMIDE

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2-{2-

20 [(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoic acid (2-1)

A 1M aqueous solution of NaOH (35.5 mL, 35.5 mmol) was added to a solution of 1-8 (7.92 g, 17.7 mmol) in MeOH (71 mL) and the resulting suspension heated at 100 °C for 1 hour. The methanol was removed *in vacuo* and saturated aqueous KH₂PO₄ solution was added and the crude product was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo* to afford 7.67 g, 100 % of 1-9 as a pale yellow solid.

MS (ESI): *m/z* = 433.2 (MH⁺).

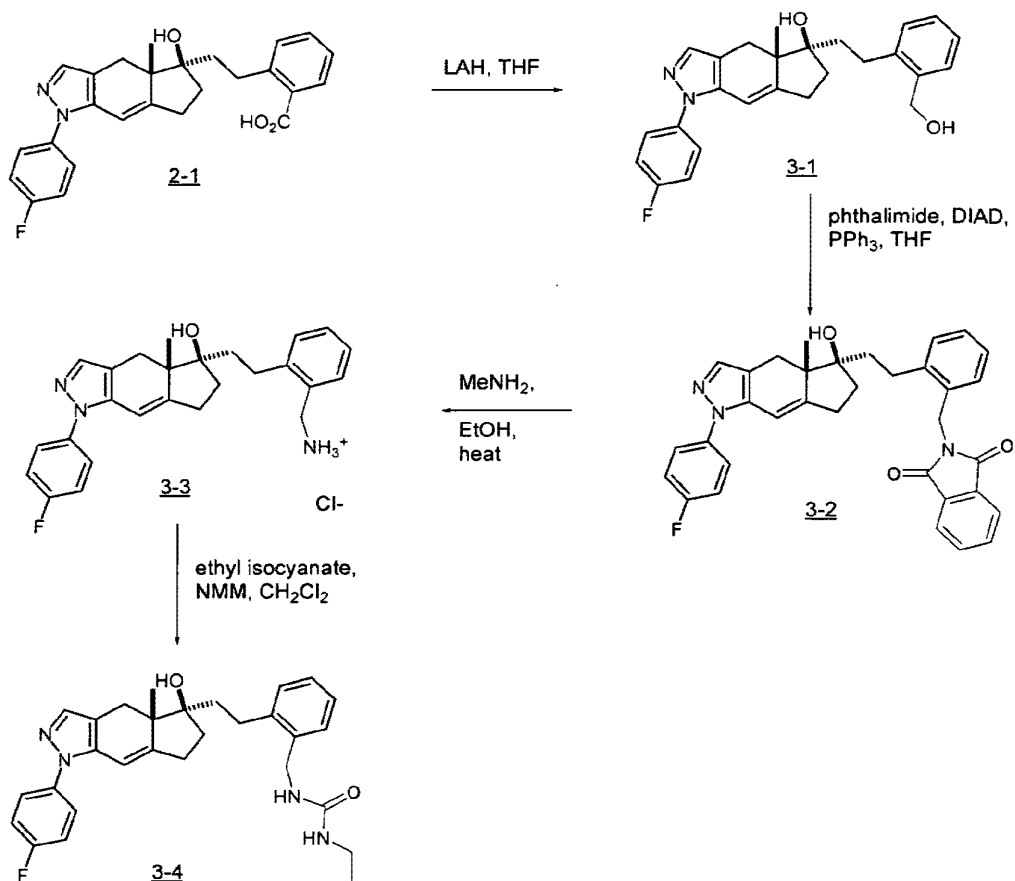
30 2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-ethylbenzamide (2-2)

A 2.0M solution of ethylamine in THF (5.55 mL, 11.10 mmol), PYBOP® (5.05g, 9.71mmol) and Hünig's Base (4.85 mL, 27.7 mmol) were added to a solution of 2-1 in anhydrous DMF (20 mL) at 0°C. The resulting solution was allowed to slowly warm to ambient

temperature and stirred overnight (20 hours). The DMF was removed *in vacuo*, water was added and the crude product was extracted with EtOAc (x3). The combined organic extracts were washed with saturated sodium bicarbonate solution, dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 10-100% [(CHCl₃/EtOAc/MeOH) (70/25/5)] in CHCl₃ afforded 3.04 g, 72 % of 2-2 as an off white foamy solid.
 MS (ESI): *m/z* = 460.2395 (MH⁺).

EXAMPLE 3

10 SYNTHESIS OF N-ETHYL-N'-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)BENZYL
UREA



(4 α S,5R)-1-(4-Fluorophenyl)-5-(2-[2-(hydroxymethyl)phenyl]ethyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-ol (3-1)

- 5 A 1 M solution of lithium aluminum hydride in THF (27.7 mL, 27.7 mmol) was added to a stirred, 0 °C mixture of 2-1 (4.0 g, 9.25 mmol) in THF (50 mL) and the resulting mixture was allowed to warm to ambient temperature and then stirred for 30 min. The resulting reaction was heated at reflux for 1 hour cooled, diluted with aqueous ammonium chloride (saturated), and then extracted with ethyl acetate. The combined organic fractions were washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*.
- 10 Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 3.2 g, 83% of 3-1 as a white solid.
- MS (ESI): m/z = 419.13 (MH⁺).

2-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)benzyl)-1H-isoindole-1,3(2H)-dione (3-2)

- 15 A solution of diisopropyl azodicarboxylate (1.6 mL, 9.03 mmol) was added to a solution of 3-1 (3.15 g, 7.53 mmol), phthalimide (1.33 g, 9.03 mmol), and triphenylphosphine (2.37 g, 9.03 mmol) in THF (35 mL) at 0 °C and the resulting solution warmed to ambient temperature and then stirred for 30 min. A solution of aqueous sodium carbonate (5 %, 100 mL)
- 20 was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 4.0 g, 97% of 3-2 as a white solid.
- MS (ESI): m/z = 548.15 (MH⁺).

(4 α S,5R)-1-(4-Fluorophenyl)-5-(2-[2-(aminomethyl)phenyl]ethyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-ol hydrochloride (3-3)

- 25 H₂O (20 mL) followed by a 2M solution of MeNH₂ in EtOH (20 mL, 40 mmol) were added to a solution of 3-2 (4.0 g, 7.30 mmol) in EtOH (50 mL) and the resulting solution
- 30 heated at reflux. After 4 hours, the reaction was allowed to cool to ambient temperature and the EtOH was removed *in vacuo*. The mixture was diluted with EtOAc and then washed with 1N NaOH, brine, dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. The resulting residue was dissolved in 50 mL EtOH, and 50 mL sat HCl/EtOH was added. After 10 minutes

the solvent was removed *in vacuo* and the residue triturated with Et₂O to afford 3.2 g, 97% of 3-3 as the hydrochloride salt.

MS (ESI): $m/z = 418.21$ (MH⁺).

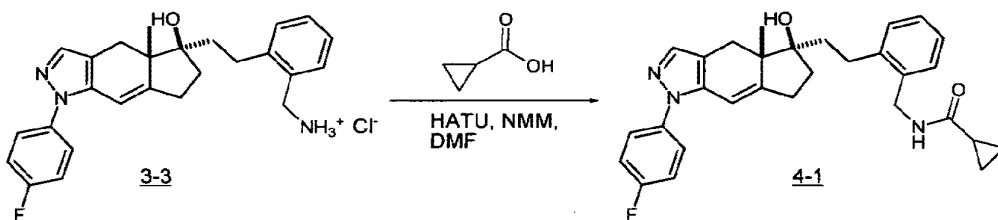
5 *N*-Ethyl-*N'*-(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)benzyl)urea (3-4)

Ethyl isocyanate (22.6 mg, 0.317 mmol) was added to a stirred solution of 3-3 (120 mg, 0.264 mmol) and 4-methylmorpholine (0.116 mL, 1.06 mmol) in CH₂Cl₂ (1 mL). The mixture was stirred for 1 hour, diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford 129 mg, 88% of 3-4 as a white solid.

HRMS (APCI): $m/z = 489.2658$ (MH⁺).

EXAMPLE 4

15 SYNTHESIS OF *N*-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)BENZYL)CYCLOPROPANECARBOXAMIDE



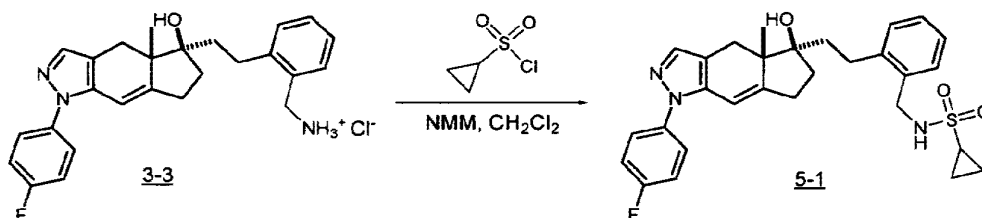
20 *N*-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)benzyl)cyclopropanecarboxamide (4-1)

HATU (120 mg, 0.264 mmol) was added to a stirred solution of 3-3 (120 mg, 0.264 mmol), cyclopropane carboxylic acid (27.3 mg, 0.317 mmol), 4-methylmorpholine (0.116 mL, 1.06 mmol) and DMF (1 mL). The mixture was stirred for 16 hours and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford 80 mg, 62% of 4-1 as a yellow foam.

HRMS (APCI): $m/z = 486.2571$ (MH⁺).

EXAMPLE 5**SYNTHESIS OF N-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(*F*)INDAZOL-5-YL]ETHYL)BENZYL)CYCLOPROPANESULFONAMIDE**

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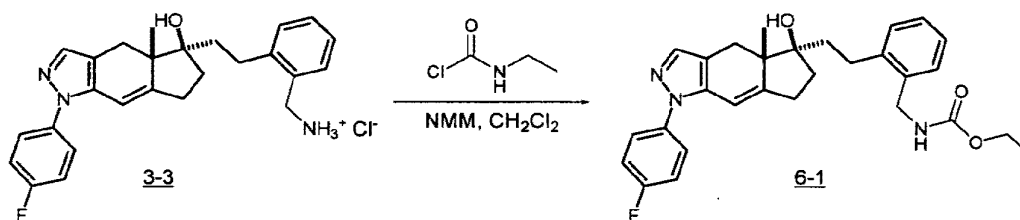
**N-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(*f*)indazol-5-yl]ethyl)benzyl)cyclopropanesulfonamide (5-1)**

Cyclopropane sulfonyl chloride (44.6 mg, 0.317 mmol) was added to a stirred solution of 3-3 (120 mg, 0.264 mmol) and 4-methyl morpholine (0.116 mL, 1.06 mmol) in CH₂Cl₂ (1 mL). The mixture was stirred for 1 hour, diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*.
 10 Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 138 mg, 58% of 5-1 as a colorless foam.
 HRMS (APCI): *m/z* = 522.2230 (MH⁺).

15

EXAMPLE 6**SYNTHESIS OF ETHYL(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(*F*)INDAZOL-5-YL]ETHYL)BENZYL)CARBAMATE**

20



Ethyl(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)benzyl)carbamate (6-1)

Ethyl chloroformate (34.4 mg, 0.317 mmol) was added to a stirred solution of 3-3 (120 mg, 0.264 mmol) and 4-methyl morpholine (0.116 mL, 1.06 mmol) in CH₂Cl₂ (1 mL). The mixture was stirred for 1 hour and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*.

Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (30 mg, 23%) of 6-1 as a colorless foam.

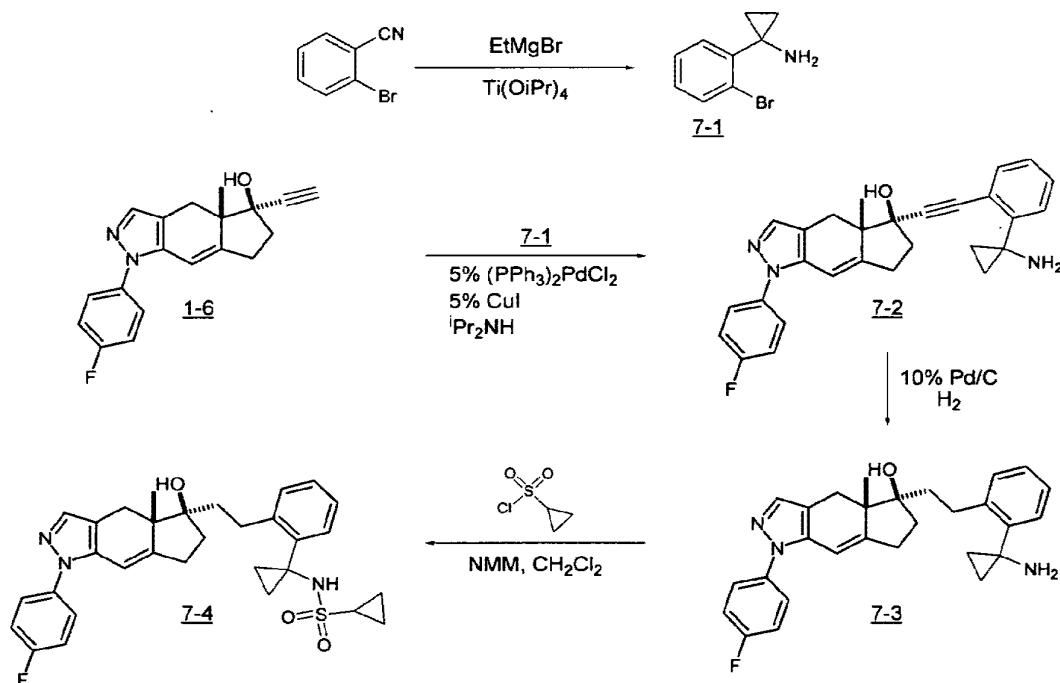
HRMS (APCI): *m/z* = 490.2525 (MH⁺).

10

EXAMPLE 7

SYNTHESIS OF N-[1-(2-{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-YL]ETHYL}PHENYL)CYCLOPROPYL]CYCLOPROPANESULFONAMIDE

15



1-(2-Bromophenyl)cyclopropanamine (7-1)

Ethyl magnesium bromide (20.14 ml, 60.4 mmol) was added dropwise to a stirred, cooled -78 °C mixture of 2-bromobenzonitrile (5.0 g, 27.5 mmol) and titanium isopropoxide (8.59 g, 30.2 mmol) in ether (100 ml) and the mixture was stirred at -78 °C for 10 minutes. The yellow solution was warmed to ambient temperature and held for 1 hour. Boron trifluoride etherate (7.8 g, 54.9 mmol) was added dropwise and the mixture was stirred for 1 hour. 1 N HCl (90 ml) was added and the mixture was stirred for 10 minutes. Added 300 ml 1N NaOH and then extracted with ether. The organic portion was washed with brine, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by flash chromatography on 80 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 0.80 g, 14 % of 7-1 as yellow oil.

MS (ESI): $m/z = 213.11$ (MH⁺).

(4 α S,5R)-5-{2-(1-Aminocyclopropyl)phenyl}ethynyl}-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (7-2)

Diisopropylamine (0.14 ml, 0.973 mmol) was added to a solution of 1-6 (300 mg, 0.973 mmol), 7-1 (206 mg, 0.973 mmol), bis(triphenylphosphine)palladium (II) chloride (34.1 mg, 0.049 mmol), and CuI (9.3 mg, 0.049 mmol) in anhydrous THF (5 ml) at ambient temperature. The resulting solution was heated at 70°C for 18 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 40 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 428 mg, 51 % of 7-2 as an orange oil.

MS (ESI): $m/z = 440.16$ (MH⁺).

(4 α S,5R)-5-{2-[2-(1-Aminocyclopropyl)phenyl]ethyl}-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (7-3)

10 % Pd/C (300 mg) was added to a solution of 7-2 (220 mg, 0.50 mmol) in EtOAc (10 ml) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 6 hours, filtered through a pad of celite and the solvent removed *in vacuo* to afford 95 mg, 43 % of 7-3 as a yellow oil.

MS (ESI): $m/z = 444.24$ (MH⁺).

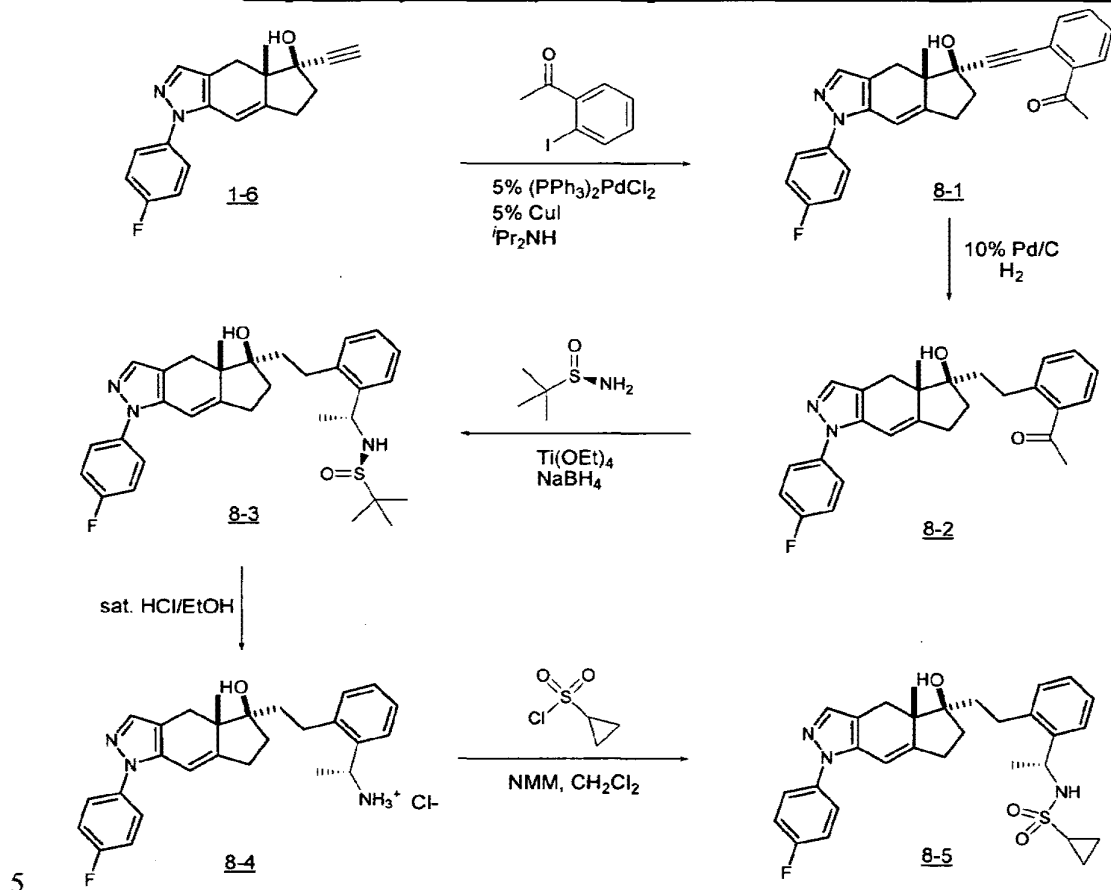
N-[1-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl)ethyl}phenyl)cyclopropyl]cyclopropanesulfonamide (7-4)

Cyclopropane sulfonyl chloride (30.9 mg, 0.220 mmol) was added to a stirred solution of 7-3 (75 mg, 0.169 mmol) and 4-methyl morpholine (0.074 ml, 0.676 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 16 hours, diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 42 mg, 45% of 7-4 as a colorless foam.
HRMS (ESI): *m/z* = 548.2386 (MH⁺).

10

EXAMPLE 8

SYNTHESIS OF N-[(1R)-1-(2-{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-YL]ETHYL}PHENYL)ETHYL]CYCLOPROPANESULFONAMIDE



1-(2-{{(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl}ethynyl}phenyl)ethanone (8-1)

Diisopropylamine (0.924 ml, 6.49 mmol) was added to a solution of 1-6 (2.0 g, 6.49 mmol), 1-(2-iodophenyl)ethanone (1.91g, 7.78 mmol), bis(triphenylphosphine)palladium (II) chloride (228 mg, 0.324 mmol), and CuI (62 mg, 0.324 mmol) in anhydrous THF (20 ml) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 2.6 g, 94 % of 8-1 as an orange oil.

10 MS (ESI): $m/z = 427.22$ (MH⁺).

1-(2-{{(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl}ethyl}phenyl)ethanone (8-2)

10 % Pd/C (1.00 g) was added to a solution of 8-1 (2.50 g, 5.86 mmol) in EtOAc (50 ml) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 6 hours, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 2.30 g, 95 % of 8-2 as a white solid.

20 MS (ESI): $m/z = 431.11$ (MH⁺).

N-[(1R)-1-(2-(2-{{(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl}ethyl)phenyl)ethyl]ethyl]-2-(R)-methylpropane-2-sulfinamide (8-3)

25 Ti(OEt)₄ (1.2 ml, 5.81 mmol) was added to a stirred solution of ketone 8-2 (500 mg, 1.16 mmol) and *R*-(+)-methyl-2-propanesulfinamide (176 mg, 1.45 mmol) and the resulting solution was heated to 80°C for 1 hour, cooled to -20°C and then NaBH₄ (44 mg, 1.16 mmol) was added. After 1 hour, MeOH (5 ml) was added (vigorous bubbling). After 10 minutes, the cooling bath was removed and 20 ml brine and celite were added to produce a thick suspension.

30 The mixture was filtered through a fritted funnel and the solids were washed with EtOAc. The organic portion was separated, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 355 mg, 57 % of 8-3 as a colorless oil.

MS (ESI): $m/z = 536.20$ (MH⁺).

(1R)-1-(2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl}phenyl)ethanaminium chloride (8-4)

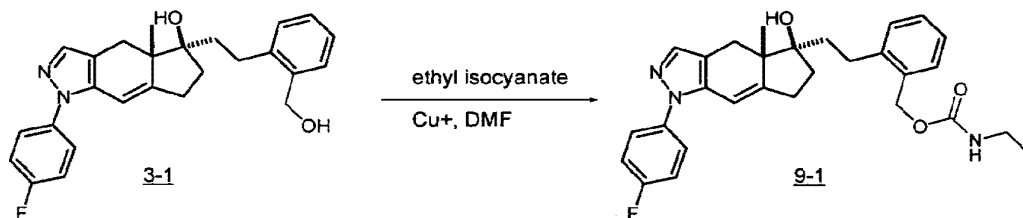
Saturated HCl/EtOH (2 ml) was added to a stirred solution of 8-3 (350 mg, 0.653 mmol) in EtOH (5 ml). The solution was stirred for 1 hour and the solvent removed *in vacuo* to afford 305 mg, 100% of 8-4 as yellow solid
MS (ESI): $m/z = 432.26$ (MH⁺).

N-[(1R)-1-(2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl}phenyl)ethyl]cyclopropanesulfonamide (8-5)

Cyclopropane sulfonyl chloride (22.5 mg, 0.160 mmol) was added to a stirred solution of 8-4 (50 mg, 0.107 mmol) and 4-methyl morpholine (0.047 ml, 0.427 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 16 hours, diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 22 mg, 38% of 8-5 as a colorless foam.
HRMS (ESI): $m/z = 536.2387$ (MH⁺).

EXAMPLE 9

20 SYNTHESIS OF 2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)BENZYL)ETHYL CARBAMATE (9-1)

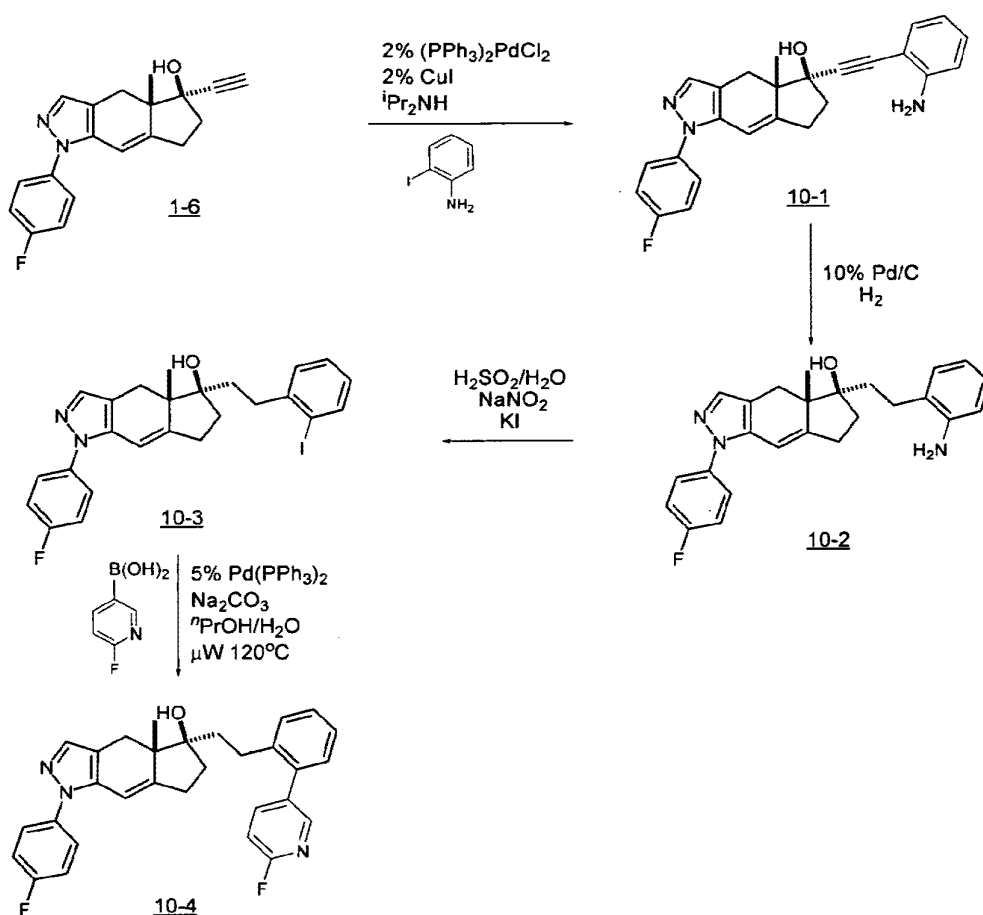


25 2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)benzyl) ethylcarbamate (9-1)

- A solution of 3-1 (100 mg, 0.239 mmol), in DMF (1 mL) was purged with nitrogen for 5 minutes and then ethyl isocyanate (20.4 mg, 0.287 mmol) and copper(I) trifluoromethanesulfonate benzene complex (72.8 mg, 0.239 mmol) were added to the degassed solution. The flask was sealed and the mixture was stirred for 5 hours then EtOAc (2 mL) was added followed by NH₄Cl solution (saturated, 1 mL) and NH₄OH (1 mL). The mixture was stirred for 5 minutes. The organic portion was separated and then was washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 30 mg, 26% of 9-1 as a yellow foam.
- 10 HRMS (APCI): $m/z = 490.2521$ (MH⁺).

EXAMPLE 10

- 15 SYNTHESIS OF (4 α S,5R)-1-(4-FLUOROPHENYL)-5-{2-[2-(6-FLUOROPYRIDIN-3-YL)PHENYL]ETHYL}-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-OL



(4 α S,5R)-5-[(2-Aminophenyl)ethynyl]-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (10-1)

- 5 Disopropylamine (1.39 mL, 9.73 mmol) was added to a solution of 1-6 (3.00 g, 9.73 mmol), 2-iodoaniline (2.56 g, 11.7 mmol), bis(triphenylphosphine)palladium (II) chloride (137 mg, 0.195 mmol), and CuI (37.0 mg, 0.195 mmol) in anhydrous THF (35 mL) at ambient temperature. The resulting solution was stirred 70°C overnight, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash
- 10 chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 3.11 g, 80 % of 10-1 as a tan solid.

MS (ESI): $m/z = 400.2$ (MH⁺).

(4 α S,5R)-5-[2-(2-Aminophenyl)ethyl]-1-(4-fluorophenyl)-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (10-2)

5 10 % Pd/C (3.31 g) was added to a solution of 10-1 (3.11 g, 7.79 mmol) in EtOAc (50 mL) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 2 hours, filtered through a pad of celite and the solvent removed *in vacuo* to afford 3.14 g, 100 % of 10-2 as a white solid.

10 MS (ESI): $m/z = 404.2$ (MH⁺).

(4 α S,5R)-1-(4-Fluorophenyl)-5-[2-(2-iodophenyl)ethyl]-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (10-3)

15 Concentrated sulfuric acid was added to a suspension of 10-2 (1.97 g, 4.88 mmol) in water (10 mL) at 0°C. A solution of NaNO₂ (337 mg, 4.88 mmol) in water (2 mL) was added and the resulting yellow solution stirred at 0°C for 15 min. A solution of KI (2.43 g, 14.6 mmol) in water (2 mL) was added and the resulting suspension was warmed to ambient temperature and stirred for 40 min. The reaction was quenched with water and the crude product extracted with EtOAc (x3). The combined organic extracts were washed with 10% w/v Na₂S₂O₃ solution,
20 dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Purification by flash chromatography on 40 g of silica, eluting with a gradient of 0-60% EtOAc in hexanes afforded 1.68 g, 67% of 10-3 as a white solid.

MS (ESI): $m/z = 515.1$ (MH⁺).

25 (4 α S,5R)-1-(4-Fluorophenyl)-5-{2-[2-(6-fluoropyridin-3-yl)phenyl]ethyl}-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (10-4)

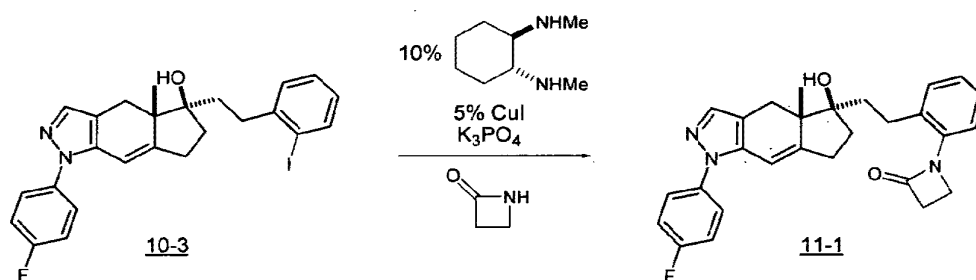
 A solution of 8-3 (30 mg, 0.058 mmol), (6-fluoropyridin-3-yl)boronic acid (9.9 mg, 0.070 mmol), Pd(PPh₃)₄ (3.4 mg, 2.9 μ mol), and Na₂CO₃ (12 mg, 0.12 mmol) in
30 ⁿpropanol:water 3:1 (0.30 mL) was heated at 120°C for 15 min in a microwave reactor. The reaction was quenched with water and the crude product extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Purification by flash chromatography on 4 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 23 mg, 81% of 10-4 as a tan solid.

MS (ESI): $m/z = 484.2$ (MH⁺).

EXAMPLE 11

SYNTHESIS OF (4 α S,5R)-1-(4-FLUOROPHENYL)-5-{2-[2-(6-FLUOROPYRIDIN-3-
YL)PHENYL]ETHYL}-4 α -METHYL-1,4,4 α ,5,6,7-
HEXAHYDROCYCLOPENTA[F]INDAZOL-5-OL

5



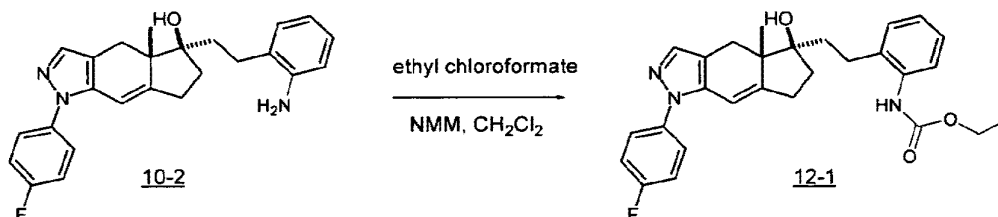
10 (4 α S,5R)-1-(4-Fluorophenyl)-5-{2-[2-(6-fluoropyridin-3-yl)phenyl]ethyl}-4 α -methyl-
1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (11-1)

A solution of 10-3 (50 mg, 0.097 mmol), azetidin-2-one (6.9 mg, 0.097 mmol),
CuI (0.93 mg, 24.9 μ mol), trans-(1R,2R)-N,N'-bismethyl-1,2-cyclohexane diamine (1.40 mg,
9.72 μ mol) and K₃PO₄ (12 mg, 0.12 mmol) in toluene (389 μ L) was heated at 100 °C for 18
15 hours. The reaction was quenched with water and the crude product extracted with EtOAc (x3).
The combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo*.
Purification by flash chromatography on 4 g of silica, eluting with a gradient of 0-100%
EtOAc in hexanes afforded 41 mg, 91% of 11-1 as a white solid.
MS (ESI): *m/z* = 458.2 (MH⁺).

20

EXAMPLE 12SYNTHESIS OF ETHYL(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)CARBAMATE

5

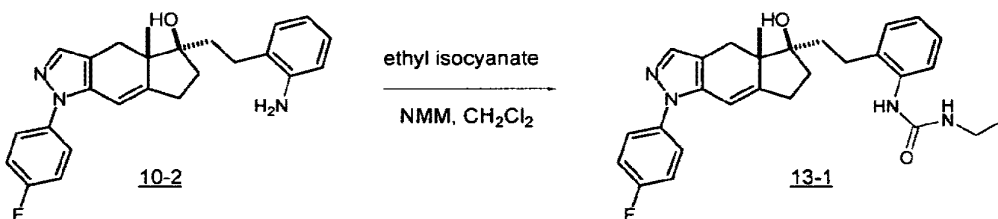
Ethyl(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)carbamate (4-2)

10 Ethyl chloroformate (13.5 mg, 0.124 mmol) was added to a stirred solution of 10-2 (50 mg, 0.124 mmol), DMAP (5 mg) and 4-methyl morpholine (0.054 ml, 0.496 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 16 hours and then was diluted with CH₂Cl₂ and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (26 mg, 44%) of 12-1 as colorless foam.

15 HRMS (ESI): *m/z* = 476.2335 (MH⁺).

EXAMPLE 13SYNTHESIS OF N-ETHYL-N'-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)UREA

20



N-Ethyl-N'-(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)urea (13-1)

Ethyl isocyanate (11.0 mg, 0.155 mmol) was added to a stirred solution of 10-2 (50 mg, 0.124 mmol), DMAP (5 mg) and 4-methyl morpholine (0.054 ml, 0.496 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 6 hours then diluted with CH₂Cl₂, washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (28 mg, 48%) of 13-1 as a colorless foam.

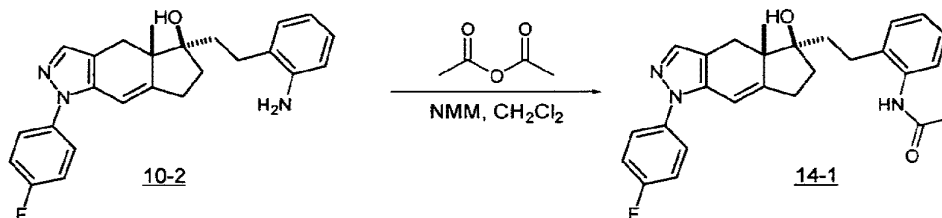
HRMS (ESI): $m/z = 475.2494$ (MH⁺).

10

EXAMPLE 14

SYNTHESIS OF N-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)ACETAMIDE

15



N-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)acetamide (14-1)

Acetic anhydride (15.2 mg, 0.149 mmol) was added to a stirred solution of 10-2 (50 mg, 0.124 mmol), DMAP (5 mg) and 4-methyl morpholine (0.054 ml, 0.496 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 6 hours and then was diluted with CH₂Cl₂ and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (22 mg, 40%) of 14-1 as a colorless foam.

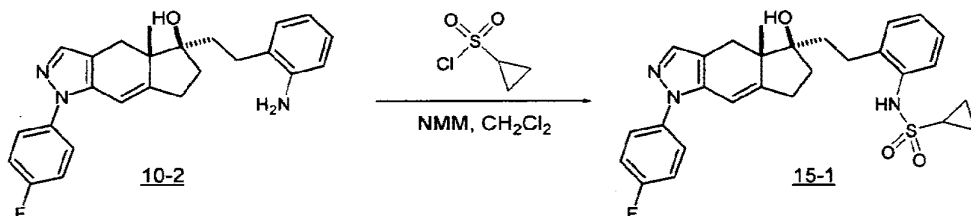
HRMS (ESI): $m/z = 446.2239$ (MH⁺).

25

EXAMPLE 15

SYNTHESIS OF N-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)CYCLOPROPANESULFONAMIDE

5

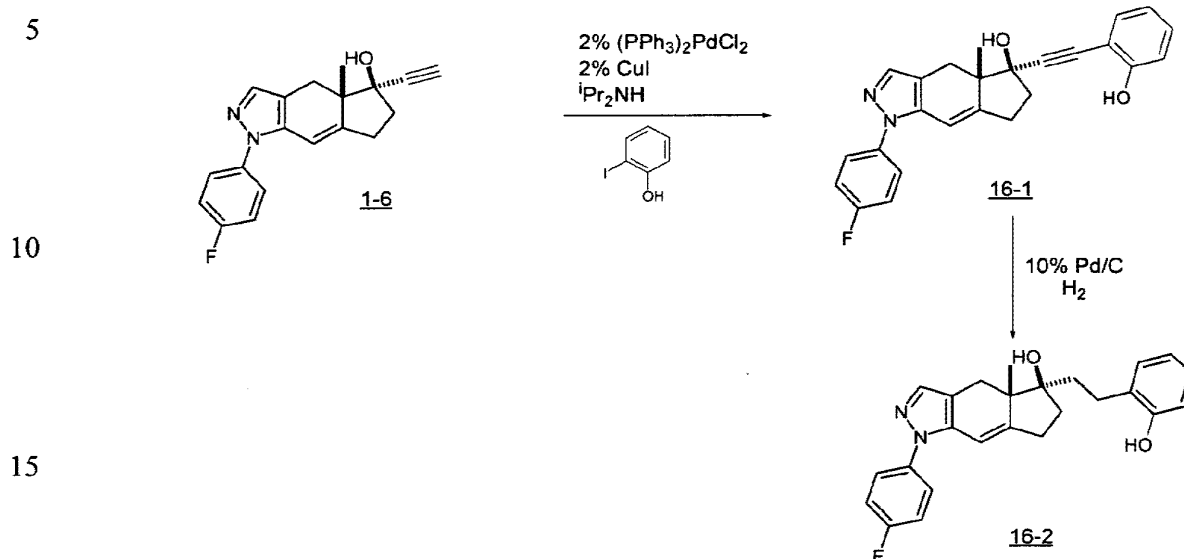


N-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)cyclopropanesulfonamide (15-1)

Cyclopropane sulfonyl chloride (20.9 mg, 0.149 mmol) was added to a stirred solution of 10-2 (50 mg, 0.124 mmol), DMAP (5 mg) and 4-methyl morpholine (0.054 ml, 0.496 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 6 hours and then was diluted with CH₂Cl₂ and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (15 mg, 24%) of 15-1 as a colorless foam.

15 HRMS (ESI): m/z = 508.2055 (MH⁺).

EXAMPLE 16

SYNTHESIS OF (4 α S,5R)-1-(4-FLUOROPHENYL)-5-[2-(2-HYDROXYPHENYL)ETHYL]-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-OL

20 (4 α S,5R)-1-(4-Fluorophenyl)-5-[2-(2-hydroxyphenyl)ethyl]-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (16-1)

Disopropylamine (116 μ L, 0.811 mmol) was added to a solution of 1-6 (250 mg, 0.811 mmol), 2-iodophenol (214 mg, 0.973 mmol), bis(triphenylphosphine)palladium (II) chloride (11.4 mg, 0.016 mmol), and CuI (3.1 mg, 0.016 mmol) in anhydrous THF (3 mL) at ambient temperature. The resulting solution was stirred 70 $^{\circ}$ C overnight, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-65% EtOAc in hexanes afforded 265 mg, 82 % of 16-1 as a white solid.

MS (ESI): m/z = 401.2 (MH⁺).

30 (4 α S,5R)-1-(4-Fluorophenyl)-5-[(2-hydroxyphenyl)ethyl]-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (16-2)

10 % Pd/C (282 mg) was added to a solution of 10-1 (265 mg, 0.662 mmol) in EtOAc (4.5 mL) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 45

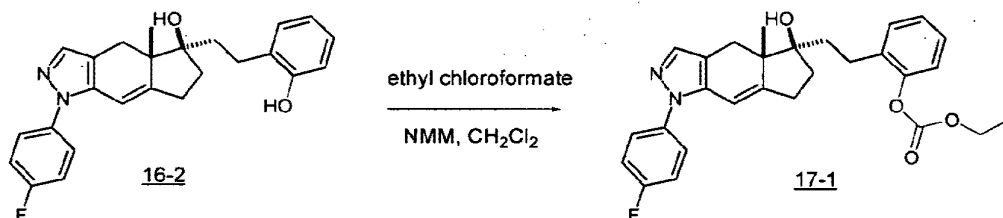
mins, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-80% EtOAc in hexanes afforded 183 mg, 68 % of 16-2 as a white solid.

MS (ESI): $m/z = 405.2$ (MH^+).

5

EXAMPLE 17

SYNTHESIS OF ETHYL-2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)CARBONATE



10

Ethyl-(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)carbonate (17-1)

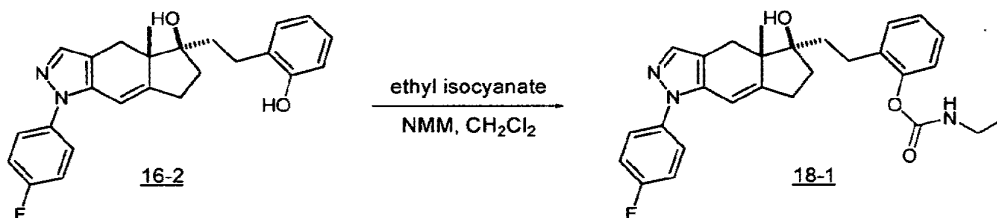
Ethyl chloroformate (13.4 mg, 0.124 mmol) was added to a stirred solution of 16-2 (50 mg, 0.124 mmol), DMAP (5 mg) and 4-methyl morpholine (0.054 ml, 0.496 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 6 hours and then was diluted with CH₂Cl₂ and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (36 mg, 61%) of 17-1 as a colorless foam.

HRMS (ESI): $m/z = 477.2173$ (MH^+).

20

EXAMPLE 18SYNTHESIS OF 2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)ETHYLCARBAMATE

5

2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)ethylcarbamate (18-1)

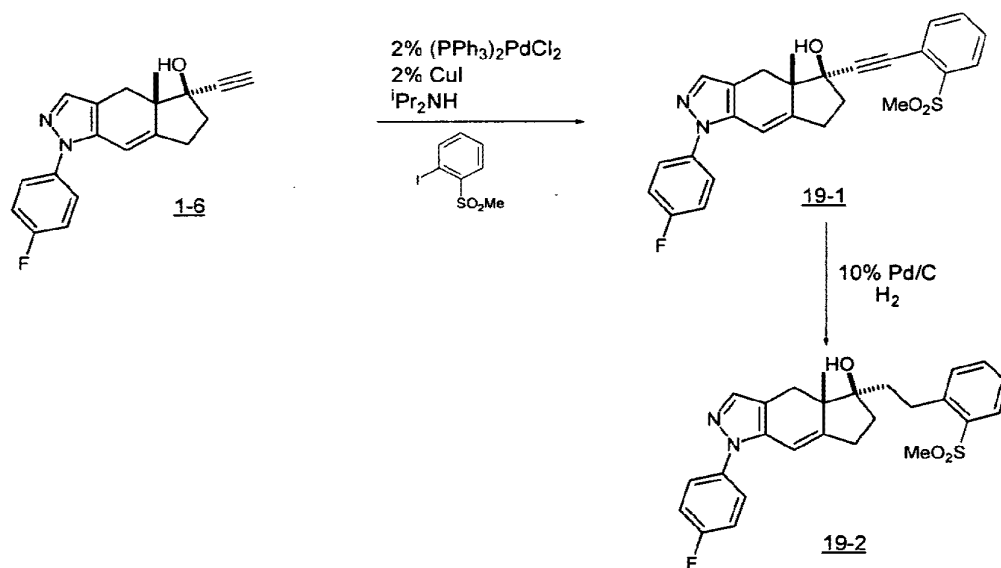
10 Ethyl isocyanate (22.6 mg, 0.317 mmol) was added to a stirred solution of 16-2 (50 mg, 0.124 mmol), DMAP (5 mg) and 4-methyl morpholine (0.054 ml, 0.496 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred for 6 hours and then was diluted with CH₂Cl₂ and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded (38 mg, 65%) of 18-1 as a colorless foam.

15 HRMS (ESI): $m/z = 476.2335$ (MH⁺).

EXAMPLE 19

SYNTHESIS OF (4 α S,5R)-1-(4-FLUOROPHENYL)-4 α -METHYL-5-{2-[2-(METHYLSULFONYL)PHENYL]ETHYL}-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-OL

5



10 (4 α S,5R)-1-(4-Fluorophenyl)-4 α -methyl-5-{2-[2-(methylsulfonyl)phenyl]ethynyl}-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (19-1)

Disopropylamine (0.048 mL, 0.334 mmol) was added to a solution of 1-6 (103 mg, 0.334 mmol), 1-iodo-2-(methylsulfonyl)benzene (113 mg, 0.401 mmol), bis(triphenylphosphine)palladium (II) chloride (23.5 mg, 0.033 mmol), and CuI (6.36 mg, 0.033 mmol) in anhydrous THF (1.0 mL) at ambient temperature. The resulting solution was stirred in an oil bath at 70°C for 1.5 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 40 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 117 mg, 83 % of the 19-1 as a white foamy solid.

MS (ESI): m/z = 463.1 (MH⁺).

20

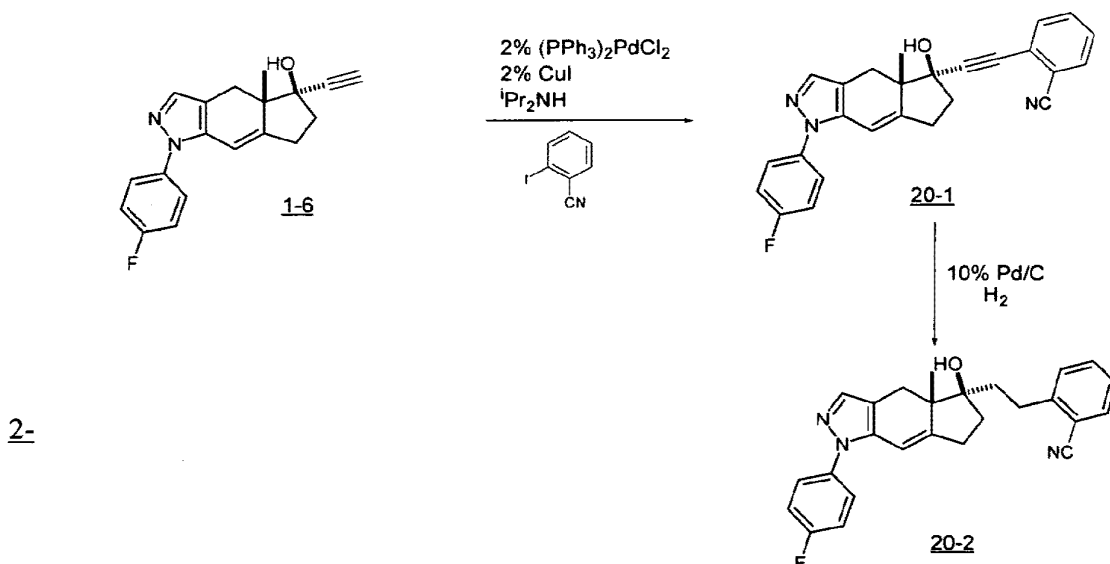
(4 α S,5R)-1-(4-Fluorophenyl)-4 α -methyl-5-{2-[2-(methylsulfonyl)phenyl]ethyl}-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (19-2)

10 % Pd/C (125 mg) was added to a solution of 19-1 (117 mg, 0.253 mmol) in EtOAc (3.5 mL) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 4 hours, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 80 g of silica, eluting with a gradient of 40-100% EtOAc in hexanes afforded 63 mg, 53 % of 19-2 as a white foamy solid.

MS (ESI): $m/z = 467.2$ (MH^+).

EXAMPLE 20

SYNTHESIS OF 2-{{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-YL]ETHYL}BENZONITRILE



{{(4 α S)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl}ethynyl}benzonitrile (20-1)

Disopropylamine (0.052 mL, 0.364 mmol) was added to a solution of 1-6 (112 mg, 0.363 mmol), 2-iodobenzonitrile (113 mg, 0.401 mmol), bis(triphenylphosphine)palladium (II) chloride (5.10 mg, 0.008 mmol), and CuI (1.38 mg, 0.008 mmol) in anhydrous THF (1.0 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 2.0 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 40 g of silica, eluting with a gradient of 0-90% EtOAc in hexanes afforded 50 mg, 33 % of 20-1 as a yellow foamy solid.

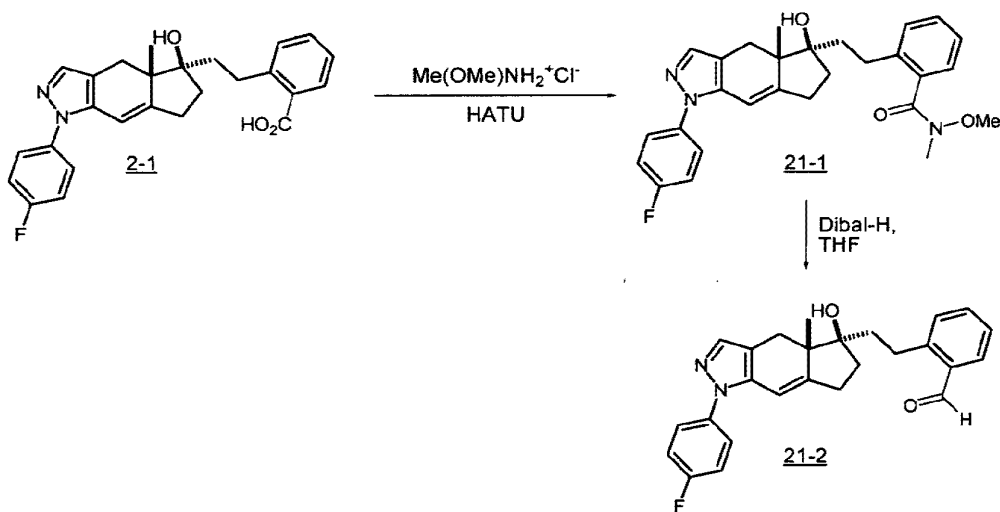
MS (ESI): $m/z = 410.2$ (MH^+).

2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzonitrile (20-2)

- 5 10 % Pd/C (52 mg) was added to a solution of 20-1 (50 mg, 0.122 mmol) in EtOAc (1.5 mL) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was slowly stirred at ambient temperature under a balloon of hydrogen for 4 hours, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-80% EtOAc in hexanes
- 10 afforded 37 mg, 73 % of 20-2 as a white foamy solid.
MS (ESI): $m/z = 414.2$ (MH^+).

EXAMPLE 21

- 15 SYNTHESIS OF 2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)BENZALDEHYDE



2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}-N-methoxy-N-methylbenzamide (21-1)

- 20 HATU (3.17 g, 8.32 mmol) was added to a stirred solution of 2-1 (3.0 g, 6.94 mmol), methoxy(methylammonium) chloride (880 mg, 9.02 mmol), 4-methylmorpholine (3.06

ml, 27.7 mmol) and DMF (20 ml). The mixture was stirred for 72 hours and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford 3.30 g, 100 % of 21-1 as a tan foam.

MS (ESI): $m/z = 476.16$ (MH⁺).

5

2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzaldehyde (21-2)

A solution of Dibal-H (15.27 ml, 15.27 mmol, 1M) was added to a solution of 21-1 (3.3 g, 6.94 mmol) in THF (3 ml) at -78 °C and the resulting solution was stirred for 2

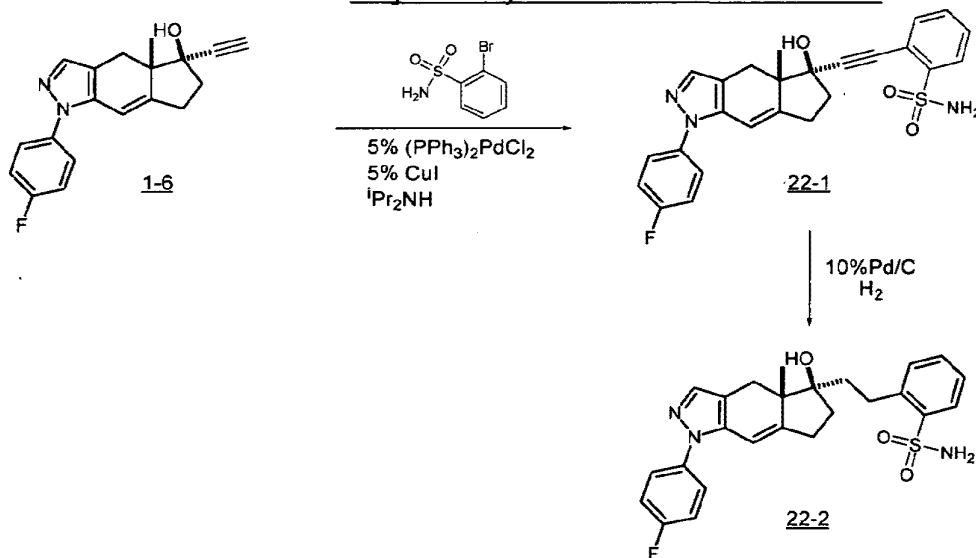
10 hours. A solution of aqueous saturated Rochelle's salt (30 ml) was added followed by the removal of the cooling bath. The mixture was stirred for 1 hour and then was extracted with CH₂Cl₂ (200 ml). The organic extracts were washed with brine, dried over anhydrous MgSO₄ and the solvent removed *in vacuo* to afford 2.60 g, 90 % of 21-2 as a tan foam.

HRMS (ESI): $m/z = 417.1969$ (MH⁺).

15

EXAMPLE 22

SYNTHESIS OF 2-{[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL}BENZENESULFONAMIDE



20

2-{[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α .5.6.7-hexahydrocyclopenta[f]indazol-5-yl]ethynyl}benzenesulfonamide (22-1)

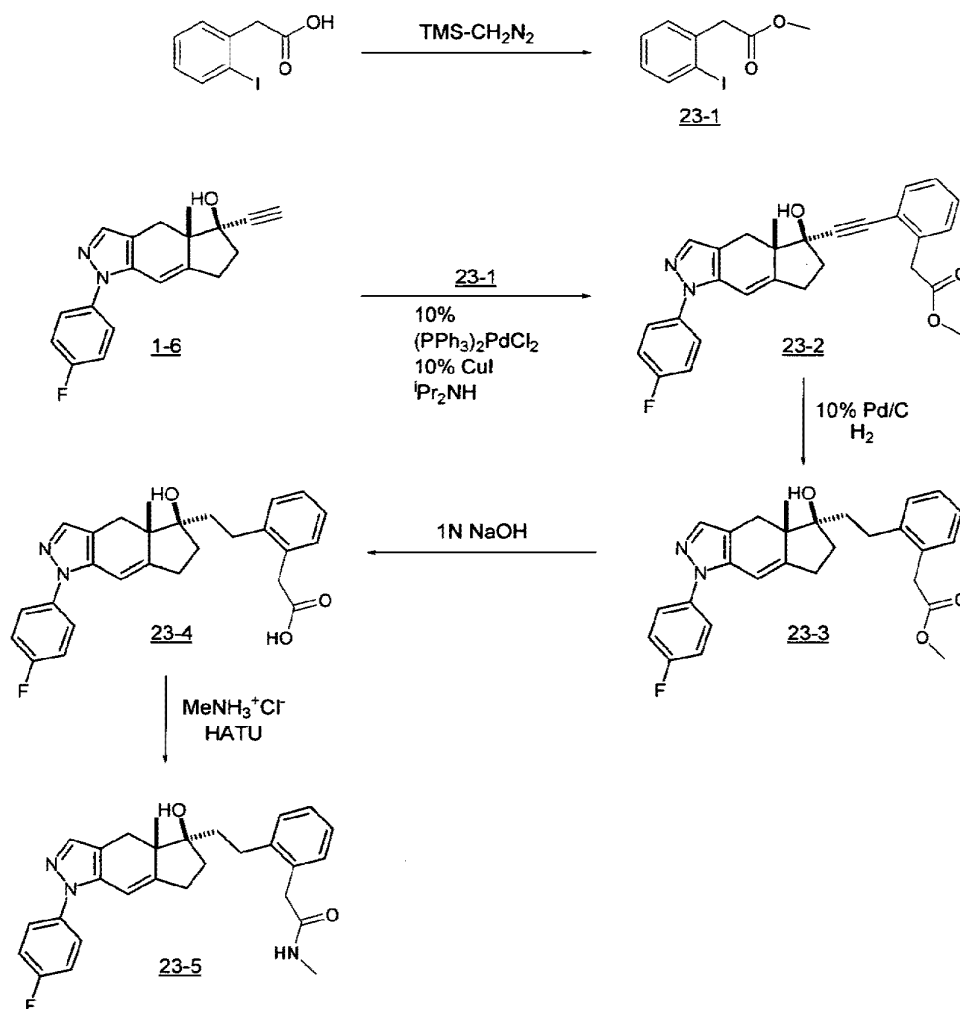
- Diisopropylamine (0.051 ml, 0.357 mmol) was added to a solution of 1-6 (110 mg, 0.357 mmol), 2-bromobenzenesulfonamide (84 mg, 0.357 mmol),
5 bis(triphenylphosphine)palladium (II) chloride (12.5 mg, 0.018 mmol), and CuI (3.4 mg, 0.018 mmol) in anhydrous THF (2 ml) at ambient temperature. The resulting solution was stirred at 60°C for 18 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 90 mg, 54 % of 22-1 as an orange oil.
10 MS (ESI): $m/z = 464.16$ (MH⁺).

2-{[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α .5.6.7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzenesulfonamide (22-2)

- 10 % Pd/C (200 mg) was added to a solution of 22-1 (80 mg, 0.173 mmol) in
15 EtOAc (5 ml) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 4 hours, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 33 mg, 41 % of 22-2 as a white solid.
20 MS (ESI): $m/z = 468.1768$ (MH⁺).

EXAMPLE 23

SYNTHESIS OF 2-(2-{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(*F*)INDAZOL-5-YL]ETHYL)PHENYL)-N-METHYLACETAMIDE

5 Methyl(2-iodophenyl)acetate (23-1)

Trimethylsilyl diazomethane (15.3 ml, 30.6 mmol, 2.0 M in diethyl ether) was added dropwise to a stirred, cooled 0°C solution of (2-iodophenyl)acetic acid (4.0 g, 15.3 mmol) and MeOH (10 ml) in CH₂Cl₂ (50 ml) and the solution was stirred at 0 °C for 1 hour. The

yellow solution was purged with nitrogen for 10 minutes. The solvent removed *in vacuo* and the residue was azeotroped with THF (3 x 25 ml) to afford 4.2 g, 100 % of 23-1 as a yellow oil.

5 Methyl-(2-([(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethynyl}phenyl)acetate (23-2)

Diisopropylamine (0.693 ml, 4.86 mmol) was added to a solution of 1-6 (1.5 g, 4.86 mmol), 23-1 (2.01 g, 7.30 mmol), bis(triphenylphosphine)palladium (II) chloride (341 mg, 0.486 mmol), and CuI (9.3 mg, 0.486 mmol) in anhydrous THF (20 ml) at ambient temperature. The resulting solution was stirred at 70°C for 2 hours, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 2.0 g, 90 % of 23-2 as an orange oil.

MS (ESI): $m/z = 457.19$ (MH⁺).

15 Methyl 2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)acetate (23-3)

10 % Pd/C (3.0 g) was added to a solution of 23-2 (2.0 g, 4.38 mmol) in EtOAc (20 ml) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 1.5 hours, filtered through a pad of celite and the solvent removed *in vacuo* to afford 1.95 g, 97 % of 23-3 as a yellow foam.

MS (ESI): $m/z = 461.20$ (MH⁺).

25 2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)acetic acid (23-4)

1M NaOH (10 ml, 10 mmol) was added to a solution of 23-3 (1.95 g, 4.23 mmol) in EtOH (20 ml) at ambient temperature. The solution was stirred at ambient temperature for 1 hour, acidified with 1N HCl and then extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo* to afford 1.9 g, 100 % of 23-4 as a yellow solid.

MS (ESI): $m/z = 447.3$ (MH⁺).

2-(2-{2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}phenyl)-N-methylacetamide (23-5)

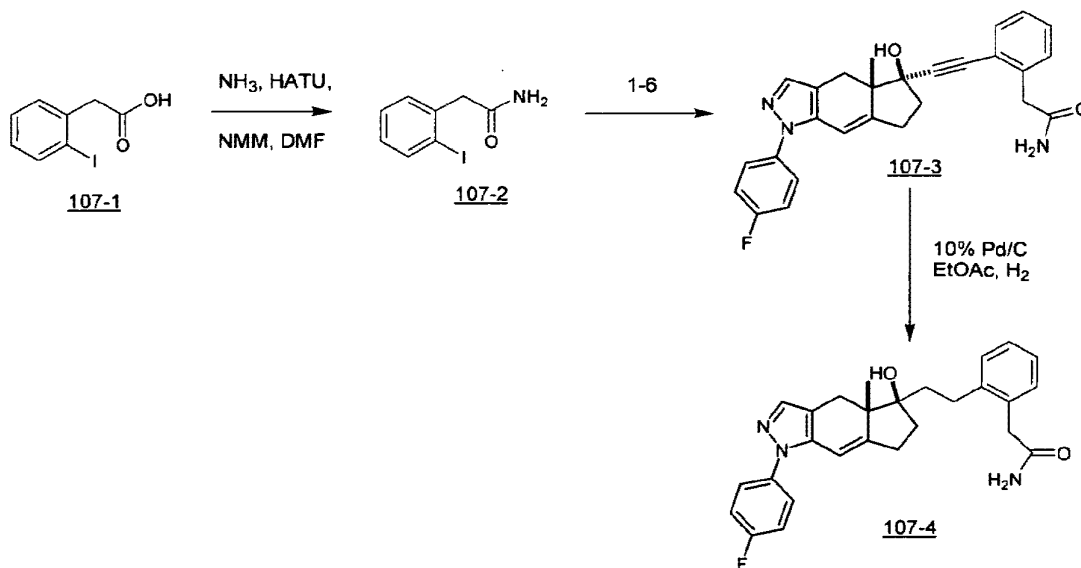
HATU (63.9 g, 0.168 mmol) was added to a stirred solution of 23-4 (75 mg, 0.168 mmol), methyl amine hydrochloride (17.1 mg, 0.210 mmol), 4-methylmorpholine (0.074 ml, 0.672 mmol) and DMF (1 ml). The mixture was stirred for 16 hours and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 80 mg, 60 % of 23-5 as a colorless solid.

MS (ESI): $m/z = 460.2395$ (MH⁺).

10

EXAMPLE 107

SYNTHESIS OF 2-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)-ACETAMIDE

2-(2-Iodophenyl)acetamide 107-2

15

HATU (50.8 g, 134 mmol) was added to a stirred solution of 107-1 (28 g, 107 mmol), NH₃ (321 ml, 160 mmol, 0.5 M/dioxane), *N*-methylmorpholine (23.5 ml, 214 mmol) in DMF (300 ml). The mixture was stirred for 16 hours and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and 2/3 solvent was

removed in vacuo. The solid was collected, washed with diethyl ether and dried in vacuo to afford 29-2 11.2g, 40.2%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ7.88 (d, 1 H, J = 8 Hz), 7.36 (m, 2 H), 7.00 (m, 1 H), 5.38 (s, 2 H),
5 3.75 (s, 2H).

Methyl(2-[(4αS,5R)-1-(4-fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethynyl)phenyl)acetamide 107-3

A mixture of 1-6 (5.0 g, 16.22 mmol), 29-2 (5.29 g, 20.27 mmol), CuI (154 mg, 0.811 mmol) diisopropylamine (2.29 ml, 16.22 mmol) and THF (50 ml) was purged with
10 nitrogen for 10 minutes. Bis(triphenylphosphine)palladium(II) chloride (569 mg, 0.811 mmol) was added and the resulting mixture heated to 70°C and then stirred for 16 hours. The mixture was allowed to cool to ambient temperature and then was diluted with Et₂O (100 ml). The mixture was filtered through a celite pad and then the solvent removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient hexanes to 5% MeOH/EtOAc
15 afforded 107-3 (5.0 g, 70%) as an orange oil.

MS (ESI): *m/z* = 442.08 (MH⁺).

2-(2-(2-[(4αS,5R)-1-(4-Fluorophenyl)-5-hydroxy-4α-methyl-1,4,4α,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)-acetamide 107-4

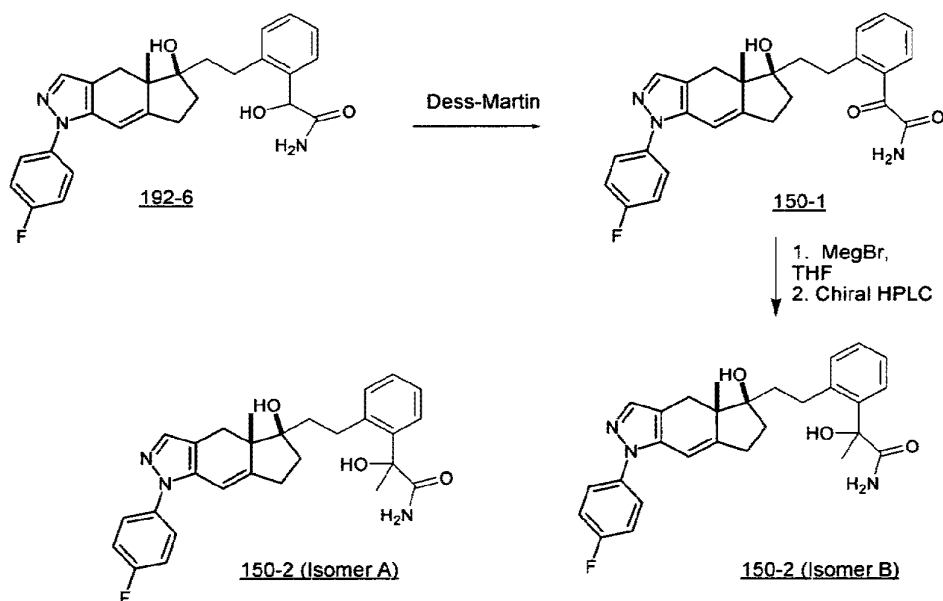
107-3 (5 g, 11.33 mmol) was dissolved in EtOAc (50 ml) followed by addition of
20 10% Pd/C (4.0 g). The mixture was stirred under 1 atm H₂ for 3.0 hour. The mixture was filtered through a pad of celite and then the EtOAc was removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient hexanes to 2.5% MeOH/EtOAc afforded 107-4 (3.8 g, 75%) as a white solid.

25 HRMS (ESI): *m/z* = 446.2236 (MH⁺).

EXAMPLE 150

SYNTHESIS OF 2-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(*F*)INDAZOL-5-YL]ETHYL)PHENYL)-2-HYDROXYPROPANAMIDE

5



2-(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(*f*)indazol-5-yl]ethyl)phenyl)-2-oxoacetamide (150-1)

10 A solution of 192-6(rac) (750 mg, 1.63 mmol) in CH₂Cl₂ (5 ml) was added to a stirred solution of Dess-Martin periodinane (758 mg, 1.79 mmol) and CH₂Cl₂ (10 ml). The solution was stirred for 1 hour and then was poured into a 1:1 aq solution of sat Na₂S₂O₃/ sat NaHCO₃ and the mixture was stirred for 10 minutes. The aqueous portion was removed and then the organic portion was washed with brine, dried over anhydrous MgSO₄, filtered and the

15 solvent was removed *in vacuo*. Purification by flash chromatography on 40 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 150-1 (545 mg, 73%) as an orange oil. MS (ESI): *m/z* = 460.07 (MH⁺).

2-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)-2-hydroxypropanamide (150-2)

A solution of methyl magnesium bromide (0.907 ml, 2.72 mmol, 3.0M diethyl ether) was added to a stirred cooled 0 °C solution of 150-1 (250 mg, 0.544 mmol) and THF (5 ml). The solution was stirred for 1 hour and then 1 M Rochelle's salt was added and the mixture was stirred for 20 minutes. The mixture was extracted with EtOAc and then the organic portion was washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 12 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded the racemic mixture. Purification by preparative HPLC, 10 cm Chiracel OD, eluting with 40% IPA/hexanes 0.1% DEA afforded faster eluting 26-2 (isomer A, 110 mg, 21.2%) as a white solid and slower eluting 150-2 (isomer B, 90 mg, 17.4%) as a white solid.

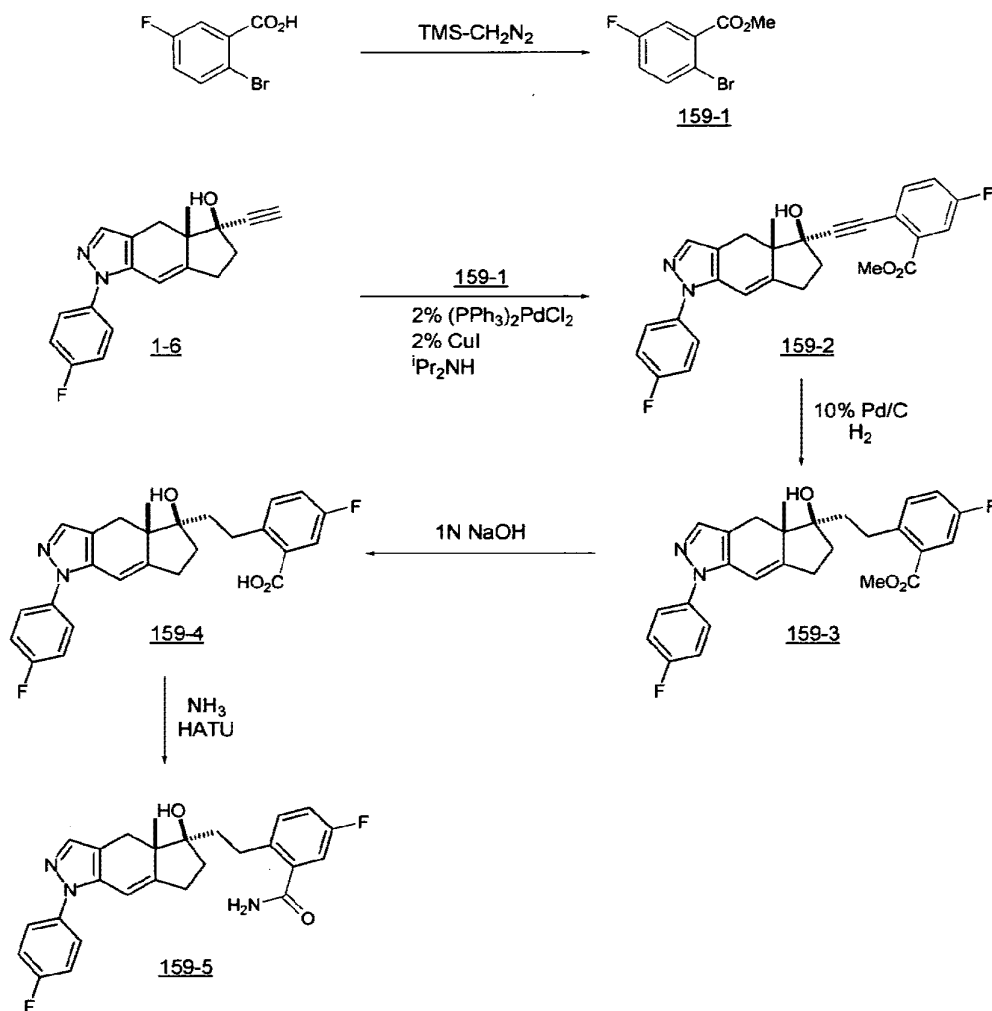
Faster eluting, HRMS (ESI): $m/z = 476.2361$ (MH⁺).

Slower eluting, HRMS (ESI): $m/z = 476.2318$ (MH⁺).

15

EXAMPLE 159**5-FLUORO-2-{2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4A,5,6,7-HEXAHYDROCYCLOPENTA[F]INDAZOL-5-YL]ETHYL}BENZAMIDEMETHYL(2-IODOPHENYL)ACETATE**

5

**Methyl 2-bromo-5-fluorobenzoate (159-1)**

Trimethylsilyl diazomethane (338 ml, 676 mmol, 2.0 M in diethyl ether) was added dropwise to a stirred, 0°C solution of 2-bromo-5-fluorobenzoic acid (74 g, 338 mmol) in MeOH (676ml) until a yellow color persisted. Acetic acid was added dropwise until the yellow

color dissipated. The solvent was removed *in vacuo*, and the residue was dissolved in CH₂Cl₂, then filtered through a plug of silica gel, eluting with CH₂Cl₂. The solvent was removed *in vacuo* to afford 77 g, 98 % of 23-1 as a yellow oil.

5 Methyl 5-fluoro-2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethynyl}benzoate (159-2)

Diisopropylamine (14 ml, 97 mmol) was added to a solution of 1-6 (30 g, 97 mmol), 159-1 (27 g, 117 mmol), bis(triphenylphosphine)palladium (II) chloride (1.36 g, 1.95 mmol), and CuI (371 mg, 1.95 mmol) in anhydrous THF (354 ml) at ambient temperature. The resulting solution was stirred at 80°C for 1 hour, then diluted with diethyl ether, filtered through a pad of celite and the solvent removed *in vacuo*. Purification by flash chromatography on 1.5 kg of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 39 g, 86 % of 159-2 as a white solid.

MS (ESI): $m/z = 461.33$ (MH⁺).

15

Methyl 5-fluoro-2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoate (159-3)

10 % Pd/C (17.9 g) was added to a solution of 159-2 (19.3 g, 42 mmol) in EtOAc (559 ml) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for 1.5 hours, filtered through a pad of celite and the solvent removed *in vacuo* to afford 18.4 g, 94 % of 159-3 as a white solid.

MS (ESI): $m/z = 465.37$ (MH⁺).

25 5-Fluoro-2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzoic acid (159-4)

1M NaOH (151 ml, 151 mmol) was added to a solution of 159-3 (35 g, 75 mmol) in EtOH (300 ml) at ambient temperature. The solution was heated at 100°C for 1 hour, acidified with 1N HCl and then extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo* to afford 37 g, 100 % of 159-4 as a white solid.

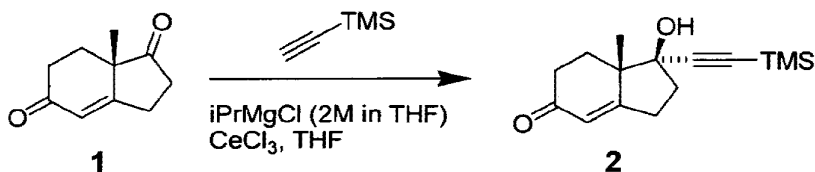
MS (ESI): $m/z = 451.10$ (MH⁺).

5-Fluoro-2-{2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzamide (159-5)

A solution of ammonia in dioxane (0.5 M, 244 ml, 122 mmol), followed by HATU (31 g, 81 mmol) was added to a stirred solution of 159-4 (36.7 g, 81 mmol) and Hunigs base (43 ml, 244 mmol) in DMF (407 ml). The mixture was stirred for 1 hour, then was diluted with EtOAc and washed with sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 1.5 kg of silica, eluting with a gradient of 0-100% CHCl₃ to CHCl₃/EtOAc/MeOH (70:20:10) afforded 28 g, 76 % of 159-5 as a white solid. The compound was dissolved in a minimal amount of boiling EtOAc, then allowed to cool slowly to ambient temperature to afford 14g of crystalline material. MS (ESI): *m/z* = 450.1998 (MH⁺).

ALTERNATE EXAMPLE 159

15 1. Alkyne addition



substrate	MW	amount	mmol	equiv
1	164	15 g	91.46	1.0
TMS alkyne	98	13 g	132.62	1.45
$iPrMgCl$ (1.8M in THF)		71.14 mL	128.05	1.4
$CeCl_3$	246	31.6 g	128.05	1.4
THF		50+150+45 mL		

20

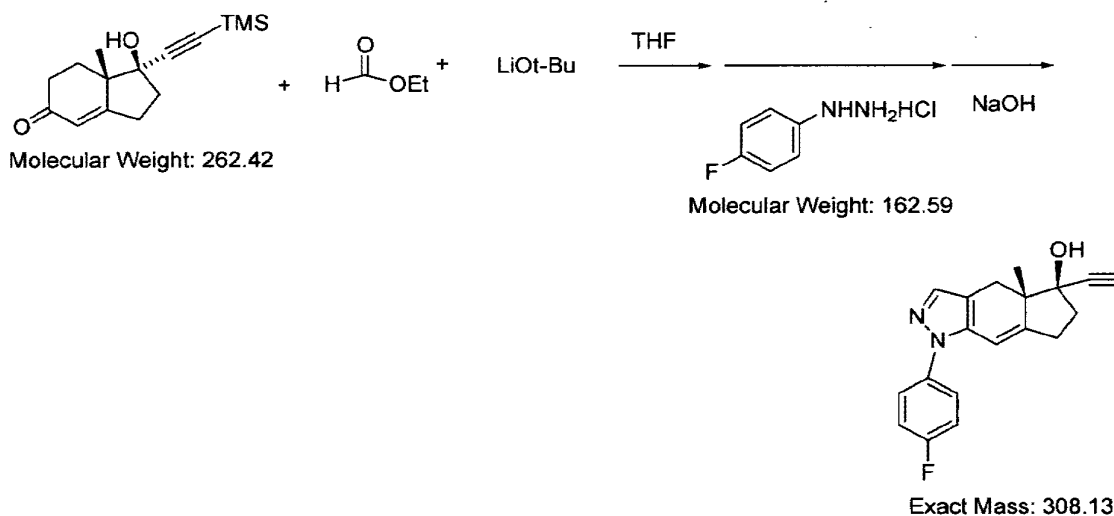
To a round bottom flask with overhead stirring, N₂ inlet, thermocouple, and reflux condenser is added THF (150 mL) and anhydrous CeCl₃ and the resulting slurry was heated to 50 °C for 4 hr then 15h at RT after which the flask is cooled to an internal temperature of -65 °C with a MeOH/dry ice bath.

Meanwhile, in a separate flask equipped with overhead stirring, N₂ inlet, and thermocouple was added THF (50 mL) and TMS alkyne and the resulting solution was cooled to an internal temperature of -5 °C. iPrMgCl (1.8M in THF) is then added portionwise, while maintaining the
5 internal temperature below 5 °C. Once all the iPrMgCl is added (1.5hr addition time), the reaction vessel is allowed to warm to room temperature and aged for 2 hr. After 2hr, the newly formed alkyne-MgCl is cooled to 10 °C and added to the CeCl₃ solution that has been previously cooled to -65 °C, keeping the internal temperature below -50 °C. Once all the alkyne-MgCl is added, the solution is aged for 1.5 hr at -60 °C. Next, the ketone in THF (45 mL) is added via an
10 addition funnel at -60 °C keeping the internal temperature below -50 °C. Once all the ketone is added, the reaction is monitored with HPLC.

When the reaction is complete, as judged by HPLC conversion of **1**, AcOH (2 mol equiv) is added (exothermic) at -50 °C and warmed to room temperature followed by addition of 30 mL of
15 water.

The biphasic solution is then transferred to a 200L extraction vessel containing water (30mL) and MTBE (300 mL). After 20 min of agitation, the aqueous layer is cut and extracted with 100 mL of MTBE. The aqueous layer is cut again, checked for losses, and discarded. The combined
20 organic layers are washed with 30 mL of fresh water then brine (30 mL), then concentrated and solvent switched to heptane to give the final composition of 1:15 of MTBE:heptane at 8-10 vol total. The resulting slurry is then aged at RT for overnight and filtered and the wetcake is washed with heptane and dried under a N₂ sweep. Isolated 18.5g of the desired product (77% yield).

2. Pyrrazole Formation



5

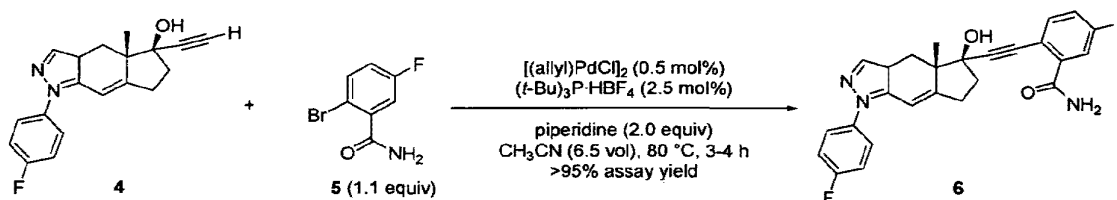
	<u>Materials</u>	<u>MW</u>	<u>Amount</u>	<u>MMoles</u>	<u>Eq</u>
10	Ketone SM	260	11 g	41.9	1.0
	Ethyl formate	74	9.4 g	127	3.0
	Li Ot-But	80	17 g	211	5.0
	THF		220 mL+50 mL		
	AcOH	60	25.4 g	423	10
15	MeOH		250 mL		
	p-F-phenylhydrazine				
	HCl salt	162.6	8.24 g	51	1.2

- 20 To a freshly prepared slurry of Li^tOBu in THF (220 mL) at 5°C is added a solution of the enone and ethyl formate in 20 mL of THF over 10 min. After aging at 5-10°C for 3h, >95% conversion is typically observed, at which point a solution of AcOH in THF (25 mL) is added slowly over 10 min, while maintaining the temperature below 25°C. During this addition, solids form almost

immediately and the batch thickens momentarily but becomes more fluid with stirring. At the end of AcOH quench, 25 mL of MeOH is then added, followed by p-F phenylhydrazine HCl salt as a solid. The reaction mixture is then heated to 60°C, aged for 1h to give a full conversion, diluted with MTBE (110 mL) and washed with 10% aqueous NaCl (110 mL). The organic layer is separated and washed one more time with 10% aqueous NaCl (100 mL). Removal of the TMS group is carried out by first diluting the organic layer with 23 mL of MeOH and 23 mL of H₂O, followed by 42 mL of 10M NaOH to bring the pH to >13. After aging at 35-50°C for 1-2h, the reaction is found complete and the batch is cooled to 25°C, washed with 110 mL of 10% aqueous brine and the organic layer is washed one more time with 170 mL of 10% aqueous brine. The organic layer is then dried over Na₂SO₄ (20g) overnight, filtered and then batch concentrated under vacuum to minimum volume (about 30 mL) using 160-200 mL of acetonitrile. Product crystallized out at this point and to this slurry is added 40 mL MTBE and then 450 L heptane over 30 min at 23 °C. After stirring for 35 min, reaction mixture is then concentrated under vacuum to remove about 20 mL of solvent. The batch is then stirred for 45 min, filtered and the wet cake is washed with 20 mL of 2:1 MTBE:heptane and air dried. The product is obtained as a brown solid in 9.1 grams (70%).

3. Coupling

20



Line	Reagent	FW	Amount	mMoles
1	Alkyne 4	308.35	9.87 gA	32.0
2	Bromide 5	218.02	7.67 g	35.2
3	Piperdine	85.15	6.39 mL	64.0
4	[(allyl)PdCl] ₂	365.89	58.8 mgA	0.160
5	(t-Bu) ₃ P·HBF ₄	290.13	232 mgA	0.800

6	CH ₃ CN	41.05	50 mL	
8	Toluene	92.14	100 mL	

Alkyne **4**, bromide **5**, acetonitrile (RM Table, line 6), and piperidine are charged successively to a round bottom flask equipped with a thermocouple, stir bar, and reflux condenser. The reagents are stirred until a reddish-brown solution is formed and the solution is degassed by 5 vacuum and nitrogen refill cycles. The phosphine ligand and palladium catalyst are then added successively and the resulting solution is degassed again. The solution is then heated to 80 °C and aged until a 99% conversion by HPLC analysis is achieved (typically 1 h). The solution is diluted with 100 mL of toluene and is then washed successively with HOAc (1.5 equiv) in 15 wt% aqueous NaCl (48 mL), saturated KHCO₃ solution (40 mL), and saturated NaCl solution (40 mL). Ecosorb 941 (2.53 g) and trithiocyanuric acid (127 mg) are added to the solution and the solution was stirred between 23-25 °C for 1 hour. The black slurry is then filtered over Solka flock (10 g) through a 15-20 micron fritted funnel. The wet cake is washed with 130 mL of 2:1 toluene:CH₃CN. The solution is transferred to a separatory funnel and washed with 15 wt% K₂CO₃ aqueous solution (38 mL) and then diluted with toluene (26.7 mL) and CH₃CN (53 mL). The organic layer is washed with saturated aqueous NaCl (38 mL) and transferred to a round bottom flask. The organic layer is assayed to contain 12.76 gA of product **6** by HPLC analysis.

4. Crystallization of Coupling Product

20

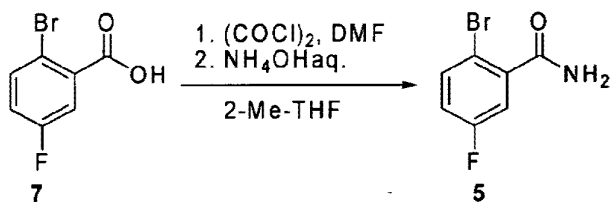
The crude solution of **6** (12.6 g) in PhMe/MeCN is concentrated under reduced pressure to remove MeCN, while maintaining the total volume of 10vol and the batch temperature at 20-25 °C. Total of 6-vol of PhMe is used during this process. At the end of the solvent switch, the resulting slurry is heated up to 90 °C and cooled slowly to 72°C. After appropriate seeding, the product started to crystallize to give a slurry which is then aged overnight. Heptane (3.3 vol) is then added and the resulting mixture is aged until 6-8% of product remained in the mother liquor. At this point, the slurry is then filtered and the wetcake is washed with cold PhMe/Heptane (3/1, 6 vol) followed by heptane (3 vol) and dried under stream of N₂ overnight.

25

The product is isolated as pale yellow solid in 13.67 g (84.4 wt%) in 92% recovery or 81% overall yield.

30

5. Bromo Benzamide Preparation



reagents	mw	amt. used	moles	equiv
2-bromo-5-fluorobenzoic acid	219.01	49.5 g	226	1
Oxalyl chloride	126.93	21.4 mL	248.6	1.1
DMF	73.09	0.871 mL	11.3	0.05
Ammonium hydroxide	35.05	62.6 mL	927	4.1
2-Me-THF		250 mL		
Water		10 L		
1 N HCl		5 L		
Brine		10 L		
PhMe		75 L + 12 L		
Heptane		10L + 7 L + 3 L		

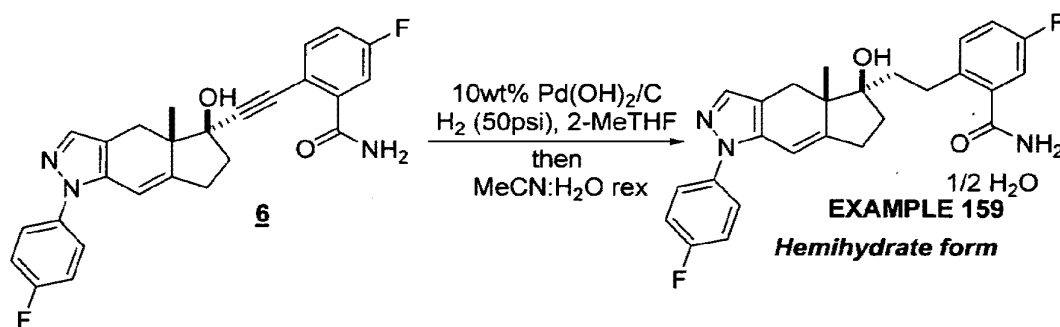
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To a RB flask equipped with an addition funnel is charged acid 7, 2-Me-THF and DMF. The solution is then cooled to 7°C and oxalyl chloride is added dropwise over 30 min at < 15 °C. After the addition is complete, the reaction mixture is warmed to rt and aged for 45 min. Upon complete consumption of the acid, the reaction mixture is then charged dropwise into another flask containing cold (9 °C) mixture of concentrated NH₄OH and 2-Me-THF over 1.5 h, while maintaining the temperature around 20-25°C. To the reaction mixture is added water (100 mL) to dissolve some solids and the resulting biphasic layer is transferred to a separatory funnel. The aqueous layer is separated and the organic layer is washed with 1 N HCl (50 mL) and with brine (100 mL). The final organic layer is then solvent switched to toluene to give a final slurry concentration of 15 vol. The slurry is then heated to 110 °C to get a clear solution, which is then

cooled slowly to RT. Crystallization is typically observed to occur at 100°C and after aging at rt overnight, heptane (10 vol) is then added, followed by a 1h of age. The suspension is then filtered and the wet cake is washed with cold 1:1 heptane:toluene and dried under a stream of N₂ to give the product in 46.9 g (94.7%).

5

6. Hydrogenation-Final Crystallization



Compounds	Amount/MW	Mmol/eq
Alkyne 6	4.86 g/445.46	10.91/1.0
Wet 20%Pd(OH) ₂ /C	56.9g/140.43	0.56/0.06
Hydrogen (H ₂)	1 atm	21.82/2.0
2-MeTHF	24 mL	5 vol
THF	24 mL	5 vol
Solka Floc	425 g	75 wt%
Ecosorb C941	114 g	20 wt%
MP-TMT	46 g	5 wt%
SiO ₂ gel	460 g	50 wt%
MeCN	~41-42 L	
H ₂ O	26 L	

10

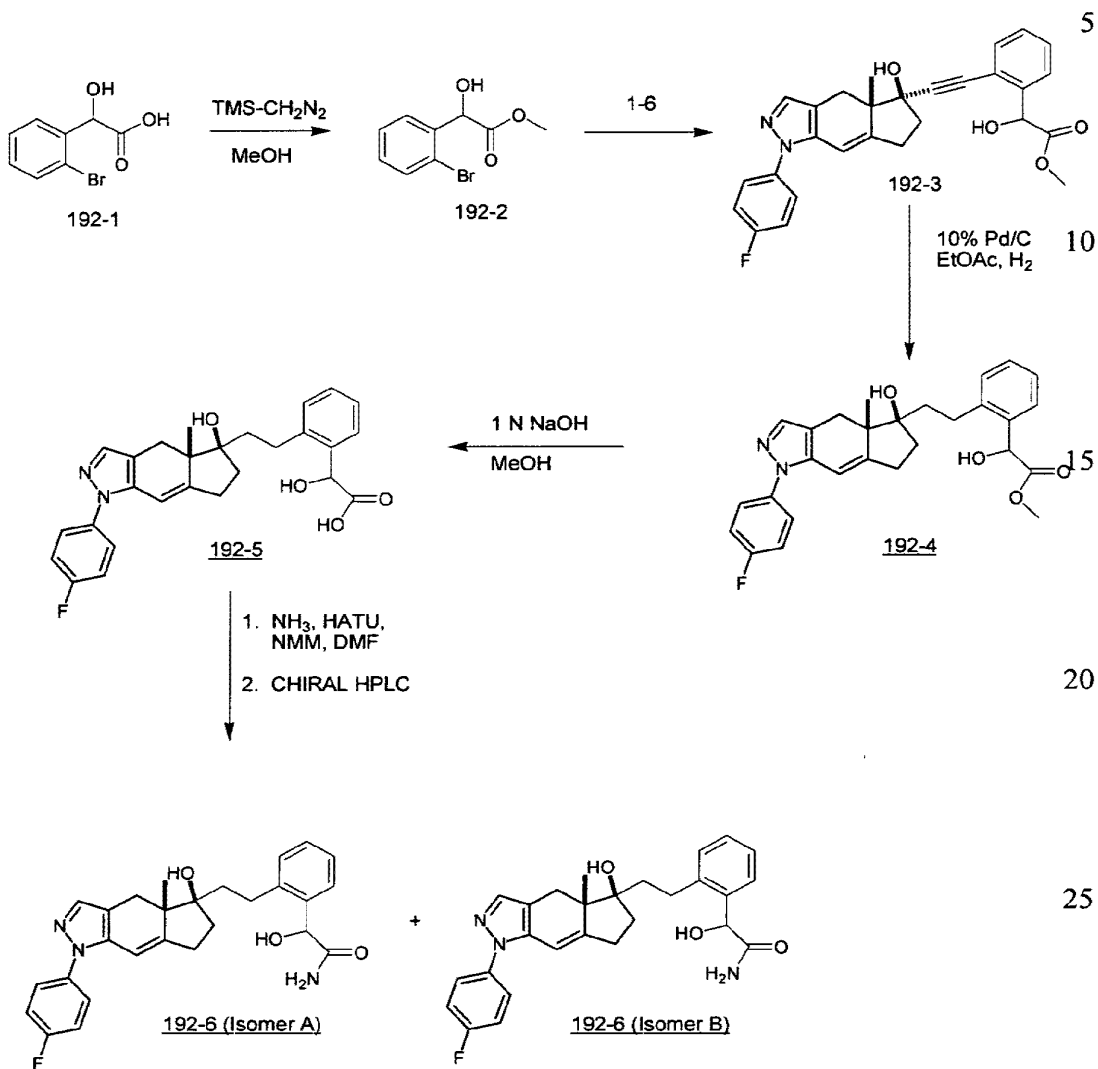
A mixture of alkyne 6 and wet 20wt% Pd(OH)₂/C in 2-MeTHF (5 vol) is exposed to 1 atm of H₂ for 6 hours, at which a complete consumption of starting is typically observed. The slurry is then diluted with THF (8 vol) and the resulting solution is filtered through Solka Floc (75wt%) and rinsed with more THF (10 vol). The combined filtrate is filtered through a 1 micron inline filter into a round bottom flask and treated with 20wt% Ecosorb C941 and 5wt% MP-TMT and aged with rigorous stirring at 25°C for 6 hours. The slurry is then filtered through 50wt% SiO₂ gel,

15

5 rinsed with 10 vol of THF and the combined filtrate is then solvent switched to MeCN to give a final slurry concentration of 13 vol. The slurry is then heated to 75°C, at which a clear yellowish solution is obtained, cooled to 72°C, seeded with 4% seeds and allowed to cool to 30°C over 5-8 hours and aged for additional 8 hours. Water (8 vol) is then added over 3 hours, while maintaining the temperature between 28-30°C. At the end of addition, the resulting slurry is allowed to cool to 4°C over 1-2h, aged for additional 1h, filtered and the wet cake is washed with cold 1:1 mixture of MeCN:H₂O. After drying at rt under a stream of N₂, 4.25 g of the product is isolated as white solid (87% yield).

EXAMPLE 192

SYNTHESIS OF 2-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)-2-HYDROXYACETAMIDE



Methyl(2-bromophenyl)hydroxy acetate (192-2)

A solution of 2 M trimethylsilyldiazomethane in diethyl ether (108 ml, 216 mmol) was added to a stirred, cooled 0 °C solution of 192-1 (25 g, 108 mmol) in CH₂Cl₂ (250 mL) and MeOH (50 ml) and the solution was stirred for 60 minutes. Nitrogen was bubbled through the solution for 10 minutes. The solvent was removed in vacuo and the residue was azeotroped with THF (3 x 25 ml) to afford 192-2 (25.5 g, 96%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, 1 H, *J* = 7Hz), 7.38 (m, 1 H), 7.34 (m, 1 H), 7.21 (m, 1 H), 5.59 (d, 1 H, *J* = 5Hz), 3.78 (s, 3H), 3.55 (m, 1 H).

Methyl(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethynyl)phenyl)(hydroxy)acetate (192-3)

A mixture of 1-6 (10g, 32.4 mmol), 192-2 (8.74g, 35.7 mmol), CuI (309 mg, 1.62 mmol) and diisopropylamine (100 ml, 701 mmol) was purged with nitrogen for 10 minutes. Tetrakis(triphenylphosphine)palladium (1.87 g, 1.622 mmol) was added and the resulting mixture heated to 90°C and then stirred for 3 hours. The mixture was allowed to cool to ambient temperature and then was diluted with EtOAc (100 ml). The mixture was filtered and the solvent removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 192-3 (12 g, 78%) as an orange oil. MS (ESI): *m/z* = 472.87 (MH⁺).

Methyl(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)(hydroxy)acetate (192-4)

192-3 (12 g, 25.4 mmol) was dissolved in EtOAc (120 ml) and then added 10% Pd/C (6.0 g). The mixture was stirred under 1 atm H₂ for 1.0 hour. The mixture was filtered through a pad of celite and then the EtOAc was removed *in vacuo* to afford 192-4 (11 g, 91%) as a yellow oil. MS (ESI): *m/z* = 476.96 (MH⁺).

(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)(hydroxy)acetic acid (192-5)

A solution of 1N NaOH (50 ml, 50 mmol) was added to a stirred solution of 192-4 (11 g, 23.08 mmol) in MeOH (120 ml) and the solution was stirred for 60 minutes. The solution was acidified with 1N HCl and then the MeOH was removed in vacuo. The residue was extracted with EtOAc and the organic portion was washed with brine, dried over anhydrous

MgSO₄, filtered and the solvent was removed *in vacuo* to afford 192-5 (10.5 g, 98%) as a white solid.

MS (ESI): $m/z = 463.01$ (MH⁺).

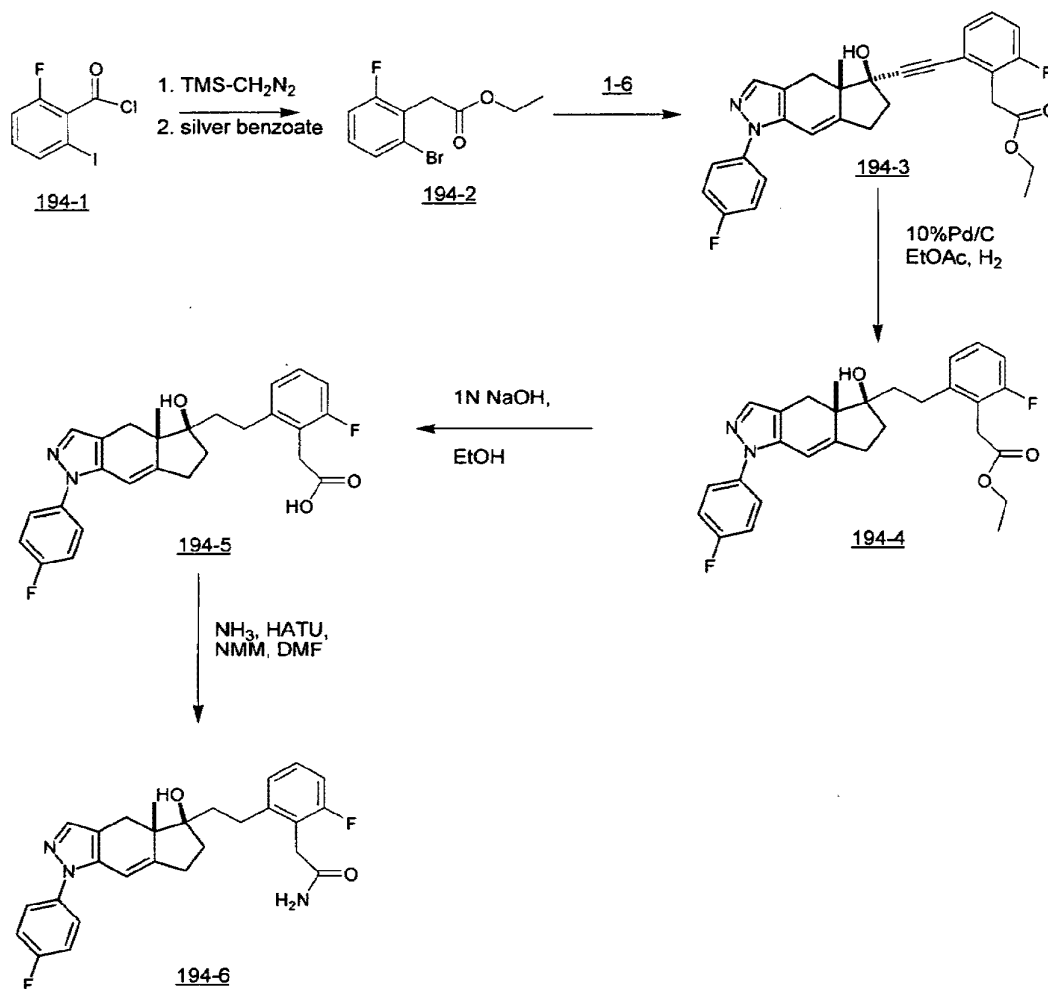
5 2-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)-2-hydroxyacetamide (192-6)

- 10 HATU (4.93 g, 12.94 mmol) was added to a stirred solution of 192-5 (5.0 g, 10.81 mmol), NH₃ (32.4 ml, 16.22 mmol, 0.5 M/dioxane), N-methylmorpholine (4.75 ml, 43.2 mmol) in DMF (100 ml). The mixture was stirred for 16 hours and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford the racemic mixture. Purification by preparative HPLC, 10 cm Chiracel AD, 2 injections, eluting with 30% IPA/hexanes 0.1% DEA afforded faster eluting 192-6 (isomer A, 1.0 g, 20.0%) as an orange solid and slower eluting 192-6 (isomer B, 2.3 g, 46%) as an orange solid.
- 15 Faster eluting, HRMS (ESI): $m/z = 462.2192$ (MH⁺).
Slower eluting, HRMS (ESI): $m/z = 462.2196$ (MH⁺).

EXAMPLE 194

SYNTHESIS OF 2-(2-FLUORO-6-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)ACETAMIDE

5

Ethyl(2-bromo-6-fluorophenyl)acetate (194-2)

194-1 (25 g, 88 mmol) was added to a stirred, cooled 0 °C solution trimethylsilyldiazomethane (65.9 ml, 132 mmol, 2M diethyl ether) and NEt₃ (18.37 ml, 132

mmol) in 1:1 THF/CH₃CN (200 mL) and the solution was kept at 0 °C for 16 hours. Nitrogen was bubbled through the solution for 10 minutes. The solvent was removed in vacuo and the residue was azeotroped with THF (3 x 25 mL). The residue was dissolved in EtOAc and then washed with H₂O, 0.1 N HCl, brine, dried over anhydrous MgSO₄ and the solvent removed in vacuo. The residue was dissolved in EtOH (100 ml) and then was treated with NEt₃ (14.7 ml, 105.6 mmol) and silver benzoate (3.95 g, 13.2 mmol). The mixture was heated to 80 °C for 10 minutes and then allowed to cool to ambient temperature. The mixture was filtered and then the solvent was removed in vacuo. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 0-20% EtOAc in hexanes afforded 194-2 (20 g, 73.6%) as a colorless oil.

10 ¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, 1 H, 8Hz), 7.07 (t, 1 H, *J* = 9 Hz), 6.99 (m, 1 H), 4.19 (m, 2 H), 3.87 (s, 2 H), 1.27 (t, 3 H, *J* = 7 Hz).

Ethyl(2-Fluoro-6-([(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethynyl)phenyl)acetate (194-3)

15 A mixture of 1-6 (4.0 g, 12.97 mmol), 194-2 (4.80 g, 15.57 mmol), CuI (247 mg, 1.30 mmol) diisopropylamine (2.02 ml, 14.27 mmol) and THF (30 ml) was purged with nitrogen for 10 minutes. Bis(triphenylphosphine)palladium(II) chloride (911 mg, 1.30 mmol) was added and the resulting mixture heated to 70°C and then stirred for 16 hours. The mixture was allowed to cool to ambient temperature and then was diluted with Et₂O (100 ml). The mixture was

20 filtered through a celite pad and then the solvent removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded 194-3 (5.5 g, 87%) as an orange oil.

MS (ESI): *m/z* = 488.87 (MH⁺).

25 Ethyl(2-fluoro-6-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)acetate (194-4)

194-3 (5.5 g, 11.26 mmol) was dissolved in EtOAc (50 ml) and then added 10% Pd/C (5.0 g). The mixture was stirred under 1 atm H₂ for 3.0 hours. The mixture was filtered through a pad of celite and then the EtOAc was removed *in vacuo* to afford 194-4 (5.2 g, 94%) as a yellow foam.

30 MS (ESI): *m/z* = 493.06 (MH⁺).

(2-Fluoro-6-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)acetic acid (194-5)

A solution of 1N NaOH (25 ml, 25 mmol) was added to a stirred solution of 194-4 (5.2 g, 10.56 mmol) in EtOH (50 ml) and the solution was stirred for 2 hours. The solution was acidified with 1N HCl and then extracted with EtOAc. The organic portion was washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford 194-5 (4.75 g, 97%) as a white solid.

MS (ESI): $m/z = 465.00$ (MH⁺).

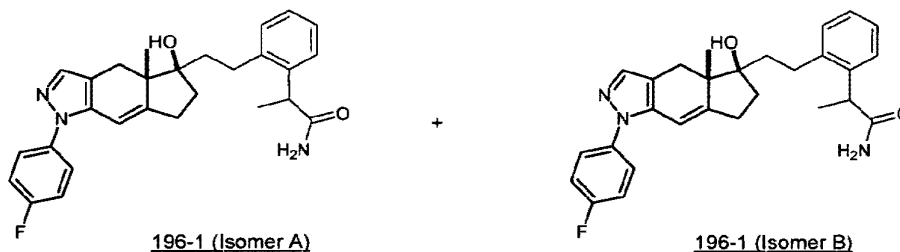
2-(2-Fluoro-6-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)acetamide (194-6)

HATU (4.42 g, 11.63 mmol) was added to a stirred solution of 194-5 (4.5 g, 9.69 mmol), NH₃ (38.8 ml, 19.38 mmol, 0.5 M/dioxane), N-methylmorpholine (4.26 ml, 38.8 mmol) in DMF (100 ml). The mixture was stirred for 16 hours and then was diluted with EtOAc and washed with H₂O, sat NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 330 g of silica, eluting with a gradient of hexanes to 5% MeOH/EtOAc afforded 194-6 (3.3 g, 73.5%) as an orange oil.

HRMS (ESI): $m/z = 464.2150$ (MH⁺).

EXAMPLE 196

SYNTHESIS OF 2-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)PROPANAMIDE



2-(2-(2-[(4 α S,5R)-1-(4-Fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)propanamide (196-1)

Compounds 196-1 were synthesized in accord with the general procedure outlined in Example 192. For the preparation of 2-(iodophenyl)propanoic acid see reference:

Journal of the American Chemical Society, **93**, 19, 4845-4850, (1971).

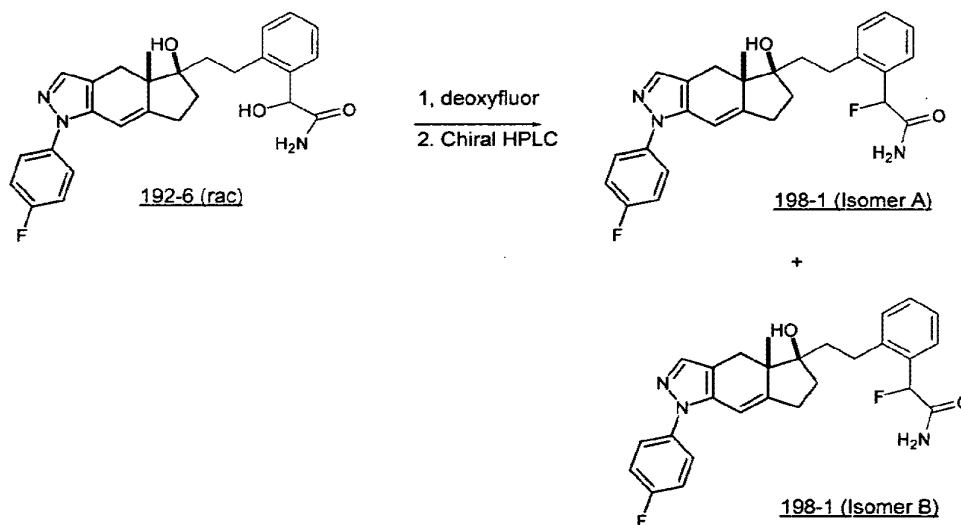
Faster eluting, HRMS (ESI): $m/z = 460.2373$ (MH^+).

5 Slower eluting, HRMS (ESI): $m/z = 460.2372$ (MH^+).

EXAMPLE 198

SYNTHESIS OF 2-FLUORO-2-(2-(2-[(4 α S,5R)-1-(4-FLUOROPHENYL)-5-HYDROXY-4 α -METHYL-1,4,4 α ,5,6,7-HEXAHYDROCYCLOPENTA(F)INDAZOL-5-YL]ETHYL)PHENYL)ACETAMIDE

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15 2-Fluoro-2-(2-(2-[(4 α S,5R)-1-(4-fluorophenyl)-5-hydroxy-4 α -methyl-1,4,4 α ,5,6,7-hexahydrocyclopenta(f)indazol-5-yl]ethyl)phenyl)acetamide (198-1)

192-6(rac) (250 mg, 0.542 mmol) in CH_2Cl_2 (2 ml) was added to a stirred cooled -78 °C solution of [Bis(1-methoxyethyl)-amino]sulfur trifluoride (0.150 ml, 0.813 mmol) and CH_2Cl_2 (3 ml). The solution was stirred for 3 hours and then sat. $NaHCO_3$ was added and the mixture was warmed to ambient temperature. The mixture was extracted with EtOAc and then

the organic portion was washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on 40 g of silica, eluting with a gradient of 0-100% EtOAc in hexanes afforded the racemic mixture. Purification by preparative HPLC, 2 runs, 5 cm Chiracel AD, eluting with 40% IPA/hexanes 0.1% DEA afforded faster eluting 198-1 (Isomer A, 60 mg, 23.9%) as a colorless foam and slower eluting 198-1 (Isomer B, 40 mg, 15.9%) as a colorless foam.

Faster eluting, HRMS (ESI): $m/z = 464.2122$ (MH⁺).

Slower eluting, HRMS (ESI): $m/z = 464.2117$ (MH⁺).

10 Biological Evaluation

The compounds exemplified in the present application exhibited activity in one or more of the following assays.

Ligand binding assay

15 Materials:

Binding Buffer: TEGM (10 mM Tris-HCl, 1 mM EDTA, 10% glycerol, 1 mM beta-mecaptoethanol, 10 mM Sodium Molybdate, pH 7.2)

50% HAP Slurry: Calbiochem Hydroxylapatite, Fast Flow, in 10 mM Tris, pH 8.0 and 1 mM EDTA.

20 *Wash Buffer:* 40 mM Tris, pH7.5, 100 mM KCl, 1 mM EDTA and 1 mM EGTA.
95% EtOH

Dexamethasone-methyl-³H, (DEX*); (Amersham cat# TRK645)

Dexamethasone(DEX) (Sigma, cat# D1756):

Hydroxylapatite Fast Flow; Calbiochem Cat#391947

25 Molybdate = Molybdic Acid (Sigma, M1651)

HeLa cell culture media:

RPMI 1640 (Gibco 11835-055) w/23.8
mM NaHCO₃, 2 mM L-glutamine

in 500 mL of complete media Final conc.

30 10 mL (1M Hepes) 20 mM

5 mL (200 mM L-glu) 4 mM

0.5 mL (10 mg/mL human insulin) 10 µg/mL

in 0.01 N HCl

Calbiochem#407694-S)

50 mL FBS (Sigma F2442) 10%
1 mL (10 mg/mL Gentamicin 20 µg/mL
Gibco#15710-072)

Cell Passaging

5 Cells (Hall R. E., et al., European Journal of Cancer, 30A: 484-490 (1994)) HeLa (ATCC) cultured in RPMI 1640 (Gibco 11835-055) containing 20 mM Hepes, 4 mM L-glu, 10 µg/ml of human insulin (Sigma, I-0259), 10% FBS and 20 µg/ml of Gentamicin (Gibco#15710-072) are rinsed twice in PBS. Phenol red-free Trypsin-EDTA is diluted in the same PBS 1:10. The cell layers are rinsed with 1X Trypsin, extra Trypsin is poured out, and the cell layers are
10 incubated at 37°C for ~ 2 min. The flask is tapped and checked for signs of cell detachment. Once the cells begin to slide off the flask, the complete media is added. The cells are counted at this point, then diluted to the appropriate concentration and split into flasks or dishes for further culturing (Usually 1:3 to 1:6 dilution).

15 Preparation of HeLa Cell Lysate

When the cells are 70 to 85% confluent, they are detached as described above, and collected by centrifuging at 1000 g for 10 minutes at 4°C. The cell pellet is washed twice with TEGM (10 mM Tris-HCl, 1 mM EDTA, 10% glycerol, 1 mM beta-mercaptoethanol, 10 mM Sodium Molybdate, pH 7.2). After the final wash, the cells are resuspended in TEGM at a
20 concentration of 10⁷ cells/mL. The cell suspension is snap frozen in liquid nitrogen or ethanol/dry ice bath and transferred to -80°C freezer on dry ice. Before setting up the binding assay, the frozen samples are left on ice-water to just thaw (~1 hr). Then the samples are centrifuged at 12,500 g to 20,000 g for 30 min at 4°C. The supernatant is used to set-up assay right away. If using 50 µL of supernatant, the test compound can be prepared in 50 µL of the
25 TEGM buffer.

Procedure for Multiple Compound Screening

1x TEGM buffer is prepared, and the isotope-containing assay mixture is prepared in the following order: EtOH (2% final concentration in reaction), ³H-DEX (Amersham Biosciences) and 1x TEGM. [e.g. For 100 samples, 200 µL (100 x 2) of EtOH + 4.25 µL of 1:10
30 ³H--Dex stock + 2300 µL (100 x 23) 1x TEGM]. The compound is serially diluted, e.g., if starting final conc. is 1 µM, and the compound is in 25 µL of solution, for duplicate samples, 75 µL of 4x1 µM solution is made and 3 µL of 100 µM is added to 72 µL of buffer, and 1:5 serial dilution.

25 μ L of ^3H -DEX (6 nM) trace and 25 μ L compound solution are first mixed together, followed by addition of 50 μ L receptor solution. The reaction is gently mixed, spun briefly at about 200 rpm and incubated at 4°C overnight. 100 μ L of 50% HAP slurry is prepared and added to the incubated reaction which is then vortexed and incubated on ice for 5 to 10 minutes. The reaction mixture is vortexed twice more to resuspend HAP while incubating reaction. The samples in 96-well format are then washed in wash buffer using The FilterMate™ Universal Harvester plate washer (Packard). The washing process transfers HAP pellet containing ligand-bound expressed receptor to Unifilter-96 GF/B filter plate (Packard). The HAP pellet on the filter plate is incubated with 50 μ L of MICROSCINT (Packard) scintillant for 30 minutes before being counted on the TopCount microscintillation counter (Packard). IC₅₀s are calculated using DEX as a reference.

Trans-Activation Modulation of Glucocorticoid Receptor (GRAMMER)

This assay assesses the ability of test compounds to control transcription from the MMTV-LUC reporter gene in lung adenocarcinoma A549 cells or HeLa cells, a human breast cancer cell line that naturally expresses the human GR. The assay measures induction of a modified MMTV LTR/promoter linked to the LUC reporter gene.

The routine transient assay consists of plating 7,000-25,000 cells/well of a white, clear-bottom 96-well plate. Alternatively, 384-well plates can be used at a cell concentration of 10,000 /well. The media that the cells are plated in is “exponential growth medium” which consists of phenol red-free RPMI1640 containing 10%FBS, 4mM L-glutamine, 20mM HEPES, 10ug/mL human insulin, and 20ug/mL gentamicin. Incubator conditions are 37°C and 5% CO₂. The transfection is done in batch mode. The cells are trypsinized and counted to the right cell number in the proper amount of fresh media. It is then gently mixed with the FuGene6/DNA mix and plated onto the 96 or 384-well plate, all the wells receive 100 uL or 40uL, respectively, of medium + lipid/DNA complex then incubated 37°C overnight. The transfection cocktail consists of serum-free OptiMEM, FuGene6 reagent and DNA. The manufacturer’s (Roche Biochemical) protocol for cocktail setup is as follows: The lipid to DNA ratio is approximately 2.5:1 and the incubation time is 20 min at room temperature. Sixteen to 24 hours after transfection, the cells are treated with dexamethasone to a final concentration of 10nM as well as the compound of interest, such that final DMSO (vehicle) concentration is equal to or less than 1%. Each plate also contains samples that are treated with 10nM dexamethasone alone, which is used as the 100% activity control. The cells are exposed to the compounds for 24 hours. After 24 hours, the cells are lysed by a Promega cell culture lysis buffer for approximately 30 min and

then the luciferase activity in the extracts is assayed in the 96-well format luminometer. In 384-well format, Steady-Glo (Promega) or Steady-Lite (PerkinElmer) can be used by adding an equal volume of reagent to the media present in each well. Activity induced by 10nM dexamethasone alone is set at 100% activity. Antagonist activity is calculated by determining the decrease in dexamethasone-induced activity in response to compound treatment relative to samples that were
5 treated with dexamethasone alone. Results are expressed as % inhibition of 10nM dexamethasone activity or as fold of 10nM dexamethasone activity. This transactivation assay can be performed in an agonist and antagonist mode to identify these different activities.

Activity of test compounds is calculated as the E_{max} relative to the activity
10 obtained with 300 nM dexamethasone. Activity of test compounds is calculated as the E_{max} relative to the activity obtained with 300 nM DEX. The exemplified tissue selective glucocorticoid receptor modulators of the present invention display agonist activity in this assay of greater than 5% and less than 100%, and maximal transactivation activity less than maximal transrepression activity.

15 The action of compounds is also tested in an antagonist mode (Anti-GRAMMER) in which the cells are treated with medium containing an agonist such as 10 nM DEX and the ability of agents to inhibit the activation by an agonist is measured.

Transrepression assay (GITAR)

20 This assay assesses the ability of test compounds to control transcription from the TNF α - β -lactamase reporter gene in U937 cells, a human myelomonocytic leukemia cell line that naturally expresses the human GR. The assay measures compound dependent-repression of the TNF α promoter linked to a reporter gene.

The human U937 cells that had been stably transfected with the TNF- α promoter
25 driving β -lactamase are used for this assay. U937 cells contain an endogenous glucocorticoid receptor (GR). Cells are maintained in RPMI 1640 Growth medium (Gibco Cat#11875-093) containing 25mM HEPES, 10% FBS, 2mM L-Glutamine, 1mM Sodium pyruvate, 25 μ g/ml Gentamicin (Gibco Cat#15710-064), 1:1000 2-Mercaptoethanol (Gibco Cat#21985-023) and 0.8 mg/ml G418 (Gibco Cat#10131-027). The density of the cells in the flask needs to be about
30 1×10^6 – 3×10^6 /ml at the time of harvest. Usually, the cells are split to $1.2 \sim 1.4 \times 10^5$ /ml (1:10) 3 days prior to the assay. 50,000 cells/well are plated in 96 well black-walled plates the day of assay. Test compounds are added 10 μ L/well, and cells are incubated at 37 $^{\circ}$ C for 30~45 min. For assaying compounds, first dilute 1:10 in DMSO to make 1 mM, then further dilute 1:100 in medium to make 10X stock prior to adding to the cells. Add 50ng/ml PMA (Sigma, cat# P8139)

10 $\mu\text{L}/\text{well}$ to a final concentration 5ng/ml, and 1 $\mu\text{g}/\text{ml}$ LPS (Sigma, cat# L4130) 10 $\mu\text{L}/\text{well}$ to a final concentration 100ng/ml. Incubate cells at 37°C overnight for ~18hr. PMA is stored frozen as 100 $\mu\text{g}/\text{ml}$ stock in DMSO. Dilute 1:10 in DMSO for a working stock of 10 $\mu\text{g}/\text{ml}$ and store at -20°C. For assaying, dilute the 10 $\mu\text{g}/\text{ml}$ working stock 1:200 in medium to make a 10X solution (50 ng/ml). Store frozen LPS at 1 mg/ml in PBS, dilute 1:1000 in medium to make 10X (1 $\mu\text{g}/\text{ml}$) for the assay. Add 6X loading buffer (CCF2-AM) 20 $\mu\text{L}/\text{well}$, and incubate at room temperature for 70~90 min. Read plates on CytoFluor II Plate Reader according to manufacture suggested protocols. The activity repressed by 100nM dexamethasone alone is set as 100% activity.

10

Microarray analysis

This assay assesses the ability of test compounds to modulate the transcription of endogenously expressed genes in a variety of cell types including but not limited to A549, HeLa or U937 cells. All cell culture reagents were purchased from Invitrogen Life Tech, Carlsbad CA. A549 cells were grown in phenol red-free DMEM/F12 medium supplemented with 10% FBS. Cells were grown at 37°C with 5% CO₂. Using the RNeasy Kit (Qiagen Corp, Valencia CA.), total RNA was extracted and purified from A549 cells treated with different GC compounds for 24 hours, at a fully active dose. These cells express large amount of the GR and are very responsive to GC treatment. All samples were compared against cells treated with vehicle.

15

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Expression levels of 23000 genes were measured using oligonucleotide microarrays purchased from Agilent Technologies, Inc. Each comparison was done on a pair of microarrays with reversed fluorophores. Raw image intensity data were processed according to the method described in Patent 6,351,712. The method was used to remove dye bias and to derive a Rosetta probability (p) and fold change value for each gene and each sample pair. Furthermore, for each gene an ANOVA model was constructed across all treatments to derive error estimates. P values for evaluating expression differences were computed using a Bayesian adjusted t-test that was developed by Lönnstedt and Speed (2002) and extended by Smyth (2003). A gene was declared differentially expressed in any particular comparison if it satisfied two criteria:

25

30

1. The Rosetta p value had to be less than 0.1 and the Rosetta fold change value had to be greater than 1.4 in at least one of the treatments.

2. The ANOVA p value had to be less than 0.01 and the fold change greater than 2 in the comparison under consideration.

In Vivo inflammation Assay

Intact adult (6 month old) female Sprague-Dawley rats are used in the oxazolone (OX) contact dermatitis model. Rats were sensitized on the ventral abdomen with OX on Day 0. On Days 7 and 9, a randomly-selected ear was challenged (same ear each time) with OX; the other was treated with vehicle. Daily treatment begun on Day 7 and continued for 7d with test compounds at different doses and 1.3 mpk 6-methylprednisolone or 0.1 mpk DEX as positive controls. The thickness of both ears are measured on Days 11 and 14. Necropsy occurred on Day 14. The rat is first weighed, then anesthetized in a CO₂ chamber until near death.

Approximately 5ml whole blood is obtained by cardiac puncture. The rat is then examined for certain signs of death and completeness. Tissues are dissected in a highly stylized fashion. The the following endpoints were evaluated: a) inhibiting ear inflammation induced by oxazolone, b) raising serum insulin, c) reducing serum ACTH, d) reducing spleen weight, e) reducing skin thickness, f) reducing body weight, g) increasing expression of bone-related genes with potential relationship to negative glucocorticoid effects on bone; e) changes in molecular markers that correlate with skin inflammation, skin thinning, muscle atrophy and glucose metabolism in liver. All blood samples were collected between 1330-1530 hours, ~4-5 hrs after the last compound treatment.

Primary data for this assay are left and right ear thickness. Inter-ear thickness difference (etd) is used for the estimating the level of inflammation and effectiveness of the compounds is determined by their ability to reduce the increase the thickness of the inflamed ear. Back of the rat skin thickness, spleen weight, serum insulin as well as the effects of gcs on the expression of molecular markers in skin inflammation, skin atrophy, muscle atrophy and glucose metabolism in liver are measured. Data are analyzed by anova plus fisher plsd post-hoc test to identify intergroup differences.

Results

The compounds shown in Table 1 were tested in the binding, GRAMMER and GITAR assays and demonstrated a superior activity profile. The compounds shown in Table 1 have potencies in the GRAMMER and GITAR assays (as measured by inflection points, IP) of less than 300nM concomitant with maximum activity in the GRAMMER assay of less than 60% and maximum activity in the GITAR assay of between 40 and 80%.

Compounds in the range of activities described above offer potential improvements over fuller agonists (higher Emaxes) as they may have less side effects as demonstrated in preclinical models. Among the compounds with the described range of

activities, different selectivity profiles may be observed in different animal models, which model the side effects of diabetes and glucose intolerance, skin and muscle atrophy, intraocular pressure, bone degradation, and hypertension. Compounds shown in Table 1 have demonstrated, or have the potential for such selectivity.

5

Table 1

Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	Emax (%)	IP (nM)	Emax (%)	% SEP
2	2.08	39	51	88	65	14
5	0.44	138	40	179	64	24
11	2.37	290	39	208	57	17
14	6.38	175	55	193	79	23
15	1.17	236	43	242	79	36
19	1.13	127	46	187	79	33
23	5.09	268	36	263	73	37

Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
26	1.37	39	24	123	39	15
28	3.55	48	28	65	72	43
29	1.14	95	24	190	61	37
30	1.52	81	29	127	50	21
31	0.90	93	9	183	48	39
32	0.49	134	13	277	49	36
33	1.13	62	37	123	62	25
34	5.29	128	13	208	54	41
35	3.55	60	48	170	62	14
37	0.44	65	57	81	58	1

Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
38	0.43	91	15	152	58	44
40	6.14	231	46	246	64	17
41	0.83	46	18	115	62	44
42	2.79	74	51	122	64	13
43	5.16	111	59	98	68	9
44	0.60	95	24	119	67	43
45	1.02	183	18	220	70	52
46	3.02	176	54	248	70	17
47	11.53	196	59	205	71	12
48	1.20	94	13	198	72	59

Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
49	0.81	26	25	30	72	47
51	7.05	164	30	193	73	42
52	0.80	21	45	154	74	29
55	0.92	173	23	187	76	53
57	0.61	24	37	30	77	40
59	1.83	108	40	95	77	37
61	0.58	86	35	83	79	44
62	9.58	212	23	246	79	56
83	0.56	70	21	94	54	33
84	0.62	50	23	96	60	37

Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
85	0.31	94	19	182	63	44
86	0.51	211	13	246	66	53
88	0.57	53	32	90	69	37
89	0.40	43	20	64	70	50
91	0.26	121	46	231	72	26
107	2.32	261	37	217	66	29
113	2.66	205	32	207	71	39
114	2.77	221	43	199	78	34
138	0.84	137	55	212	72	17
143	1.44	118	41	194	70	29

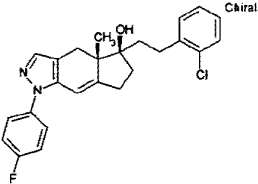
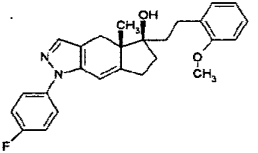
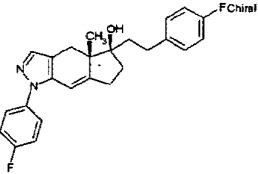
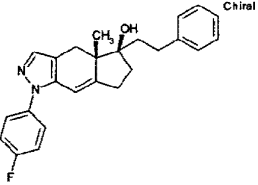
Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
144	1.32	268	40	212	70	30
148	0.67	43	57	46	75	18
150	11.00	264	38	210	67	29
151	1.74	170	43	207	76	33
152	2.60	223	44	247	77	34
156	2.90	278	47	189	69	22
157	1.50	240	45	194	63	18
159	2.96	197	37	125	73	36
160	0.94	118	30	274	72	42
163	0.17	103	48	299	70	23

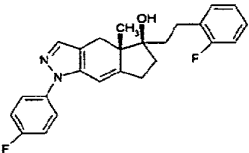
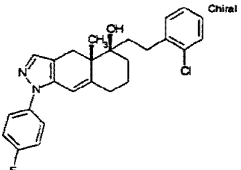
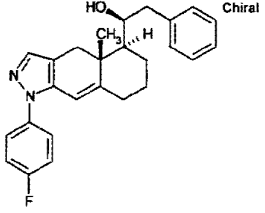
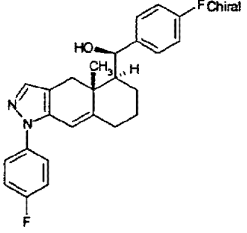
Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
168	2.16	53	58	52	77	19
170	2.12	234	24	223	66	42
172	6.59	162	41	139	78	36
174	4.76	147	36	183	77	41
185	1.93	144	39	59	80	41
189	1.55	28	49	23	80	31
191	2.51	55	49	33	78	29
194	1.48	99	38	87	78	41
196	1.80	253	20	287	40	20
197	1.41	249	46	138	67	21

Example	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP
198	2.44	187	29	197	52	23
199	4.55	83	36	77	68	32
201	5.62	47	40	40	78	38

Furthermore, the compounds previously described in the patent literature that are the most closely structurally related to the compounds described in Table 1 do not possess the superior activity profile as described above. Data for these compounds is shown in Table 2. As can be seen from a direct comparison of the data, the compounds described in Table 1 possess an unexpectedly superior activity profile as compared to the compounds of Table 2.

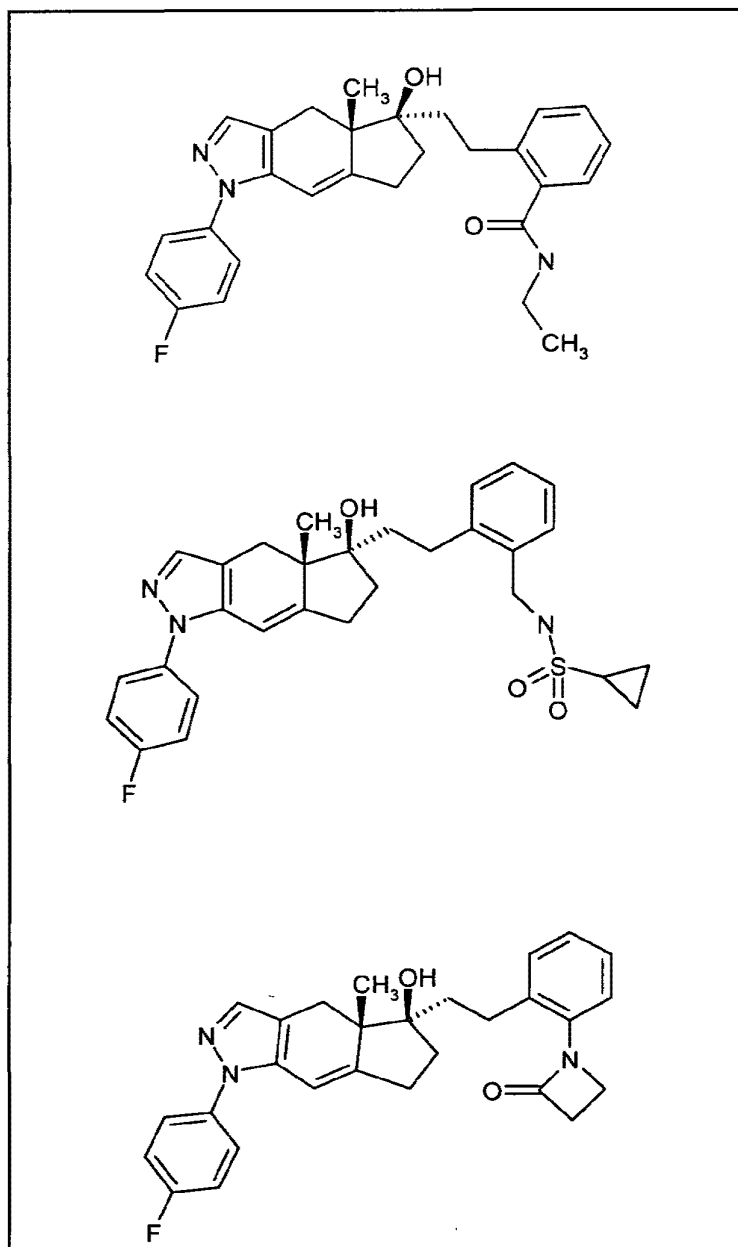
Table 2

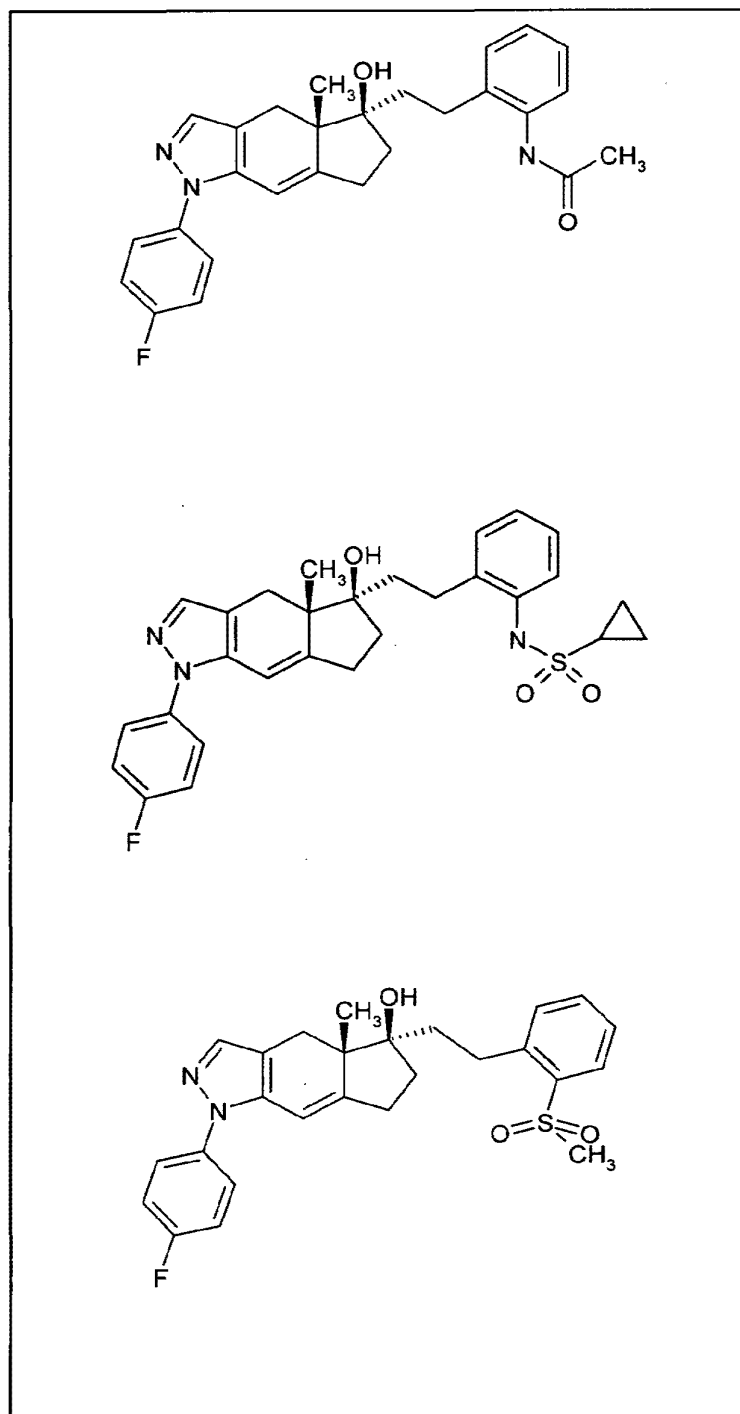
Structure	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM	
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP	
	20.72	162	98	212	91	-7	
	0.28	397	28	642	42	14	
	1.00	571	26	596	71	44	
	5.24	230	73	204	78	5	

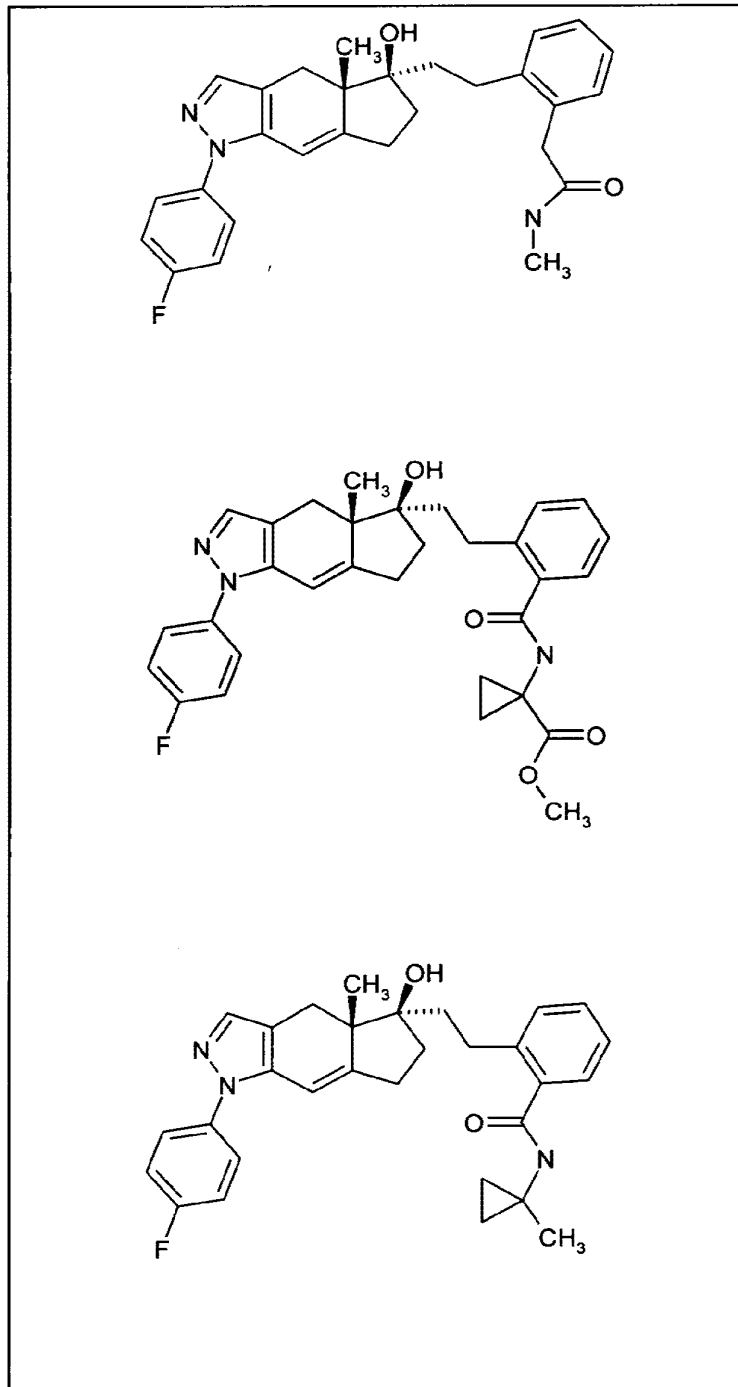
Structure	GR BIND Ki (nM)	Transactivation A549 Cells GRAMMER		Transrepression U937 Cells GITAR		GITAR > GRAMM	
		IP (nM)	E _{max} (%)	IP (nM)	E _{max} (%)	% SEP	
	2.95	215	144	175	83	-62	
	0.32	123	92	270	88	-3	
	1.27	109	85	327	71	-14	
	2.04	377	85	327	71	-14	

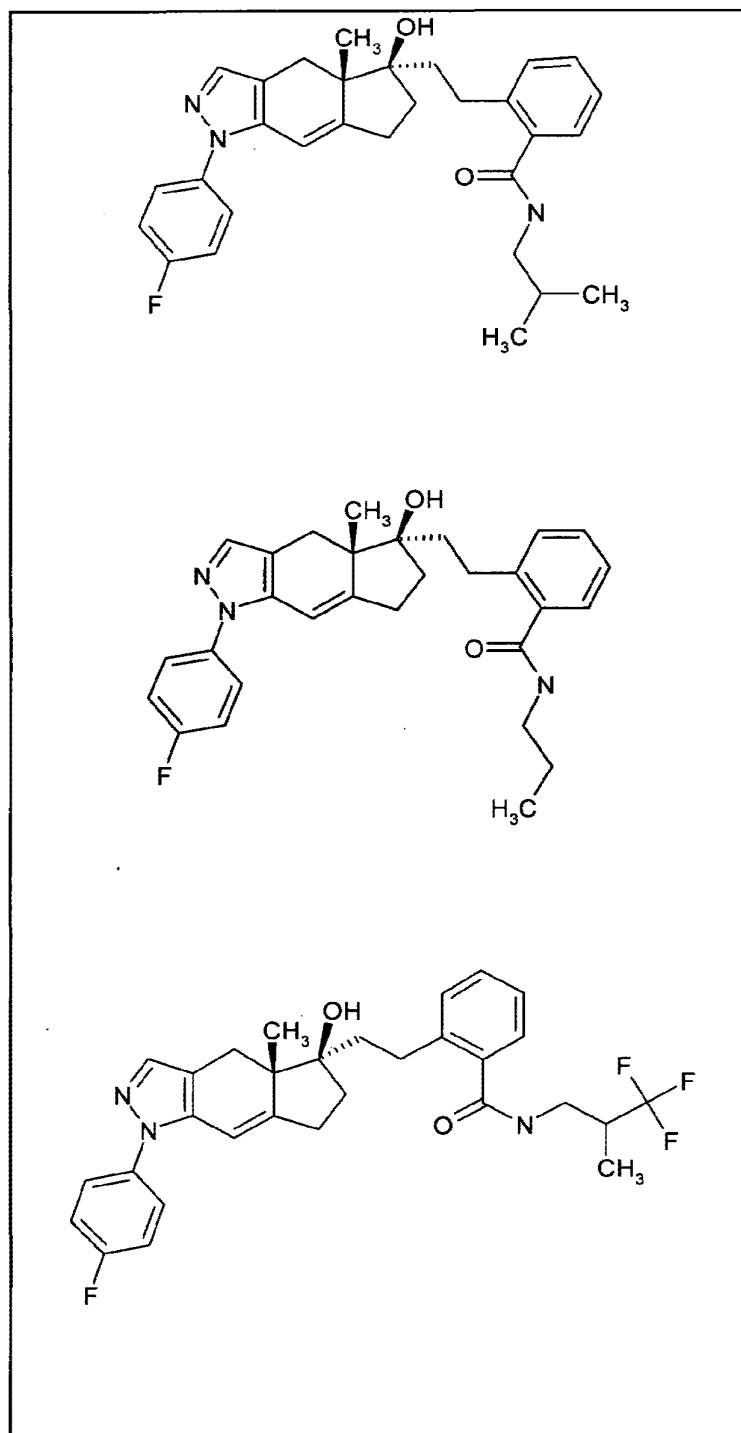
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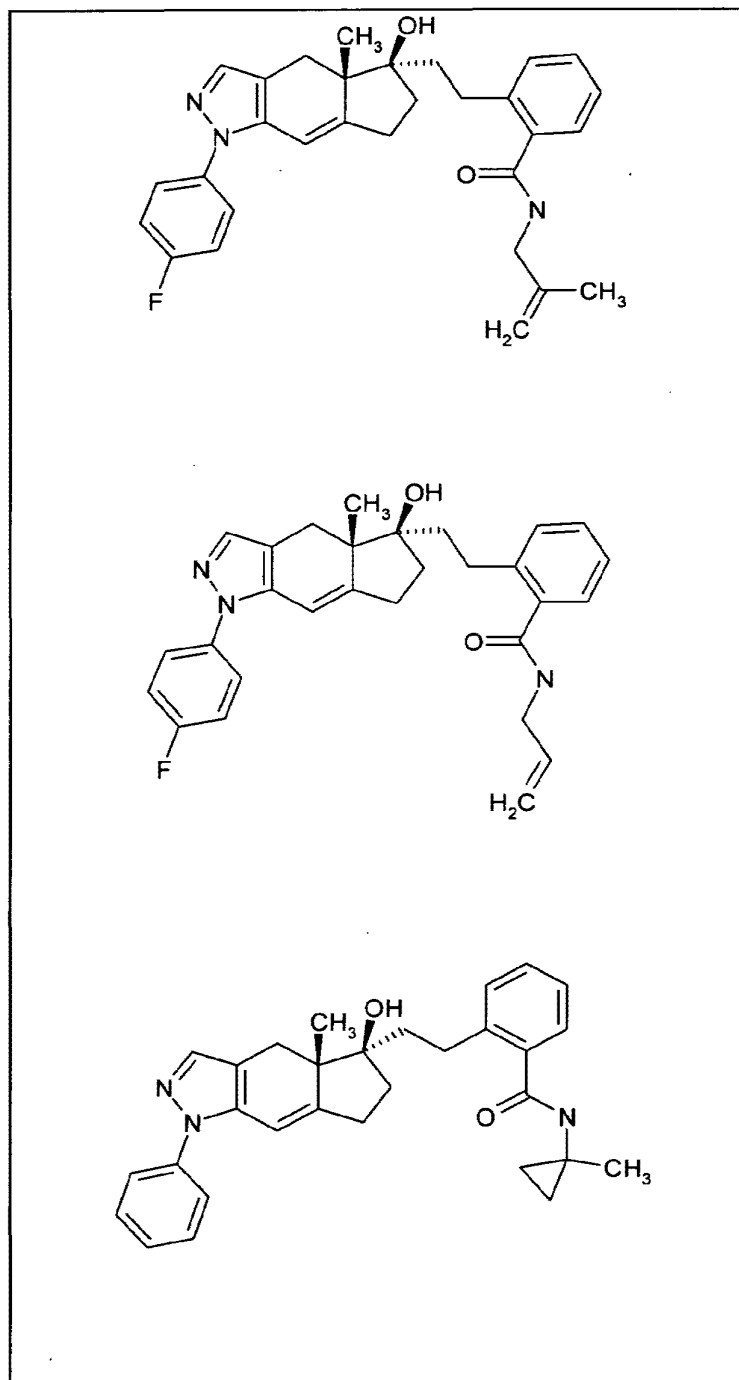
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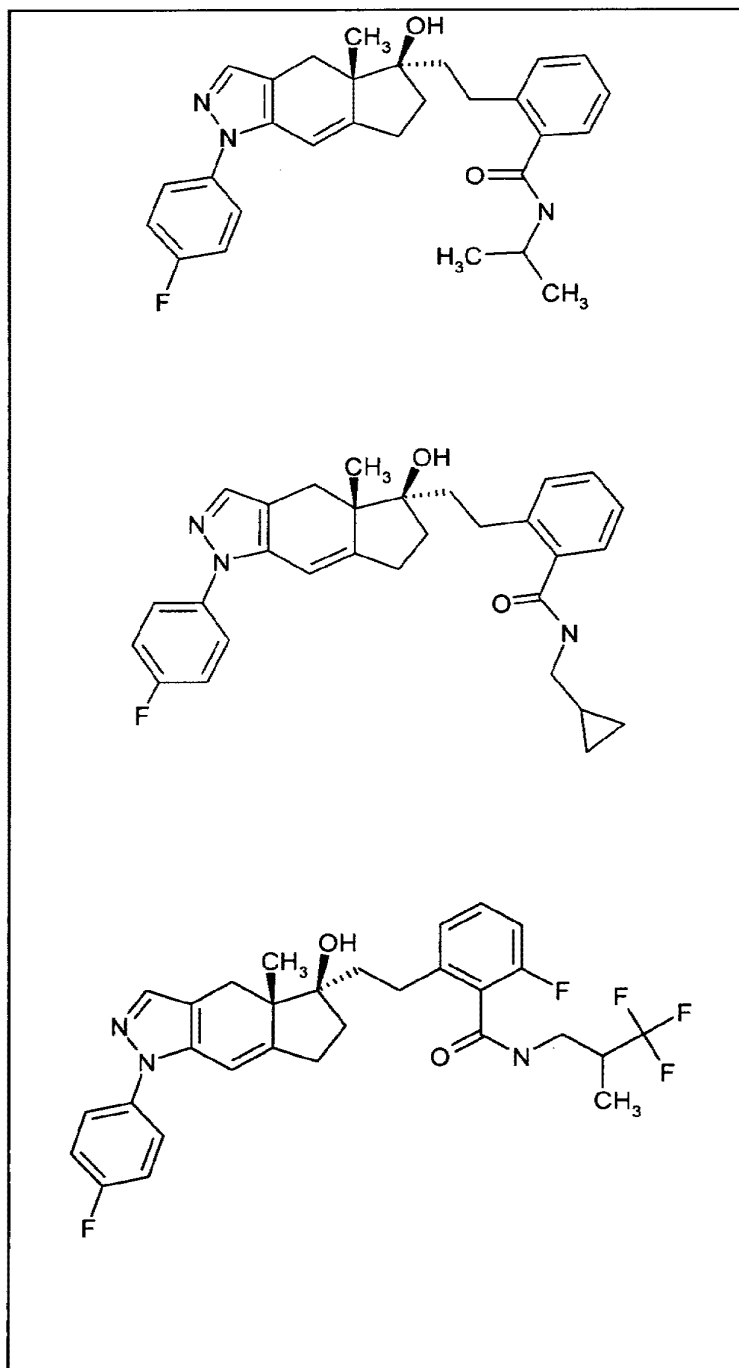


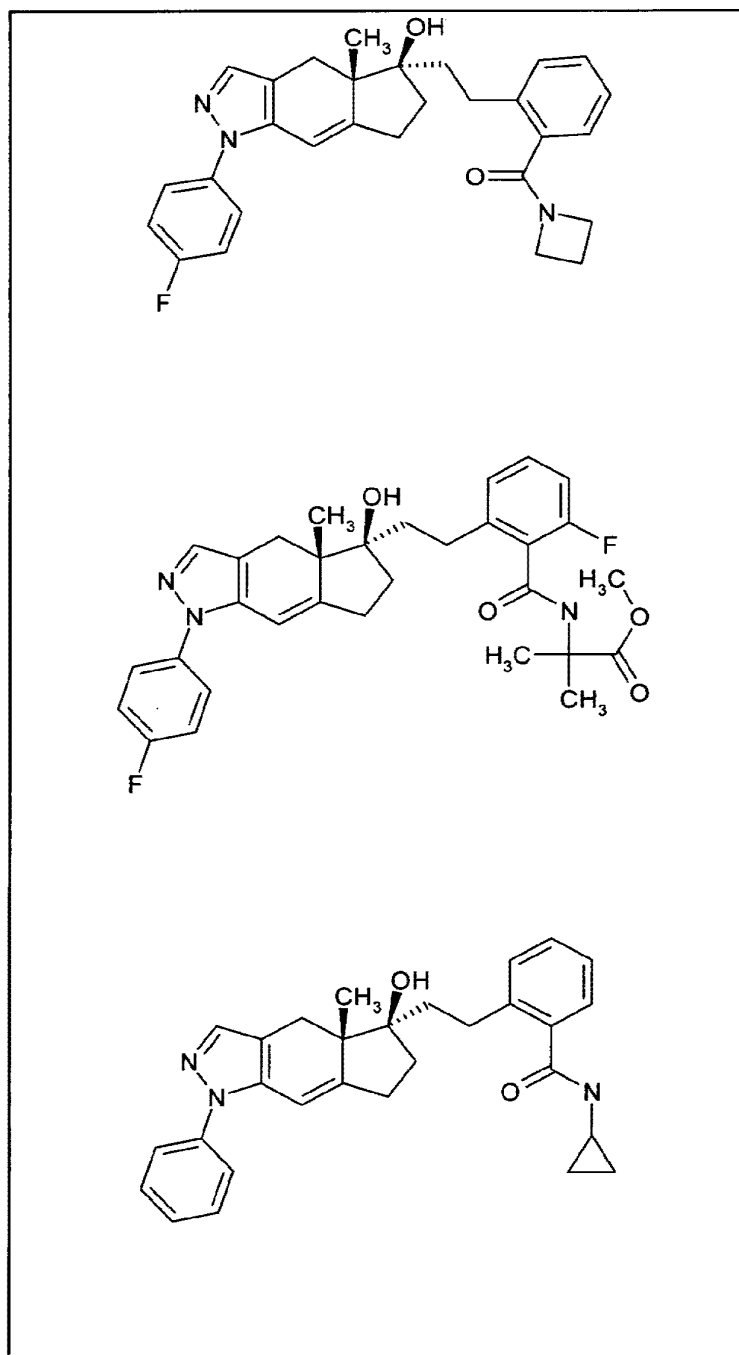


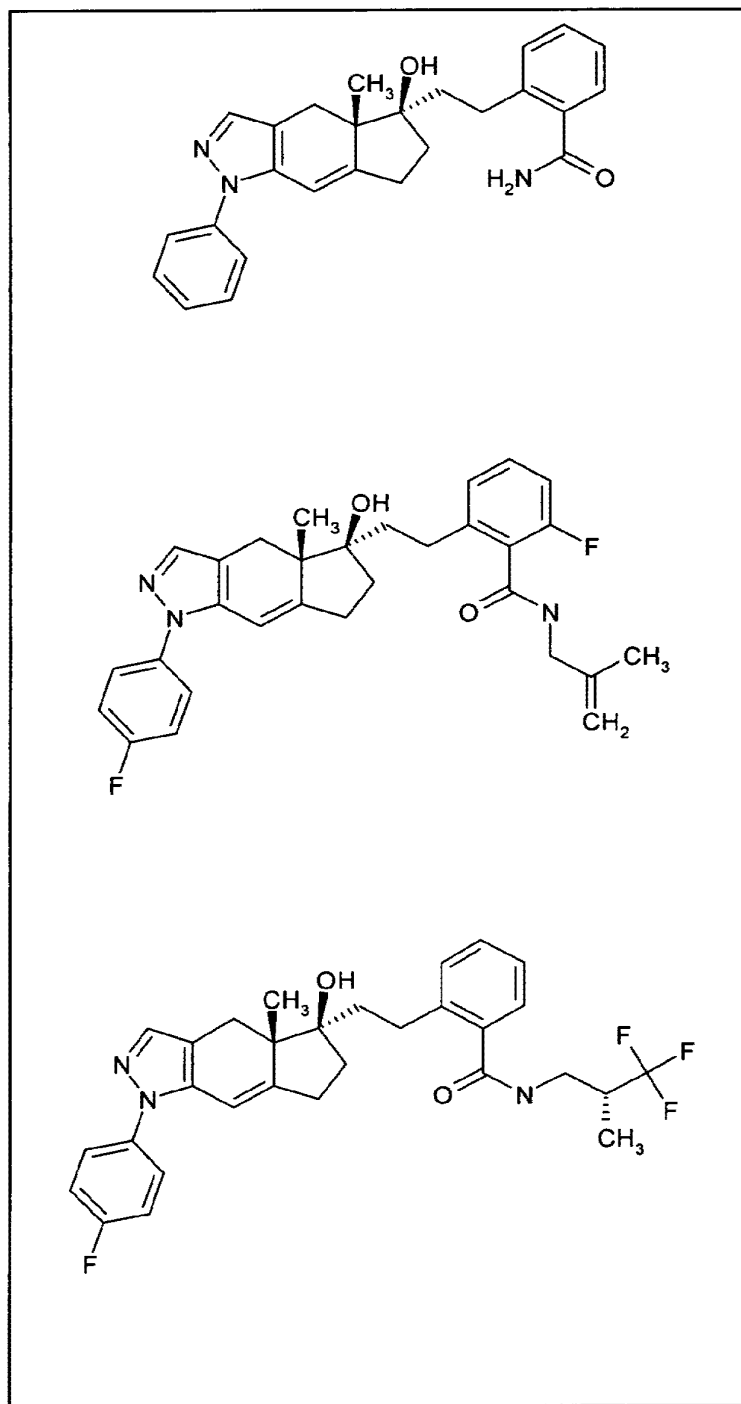


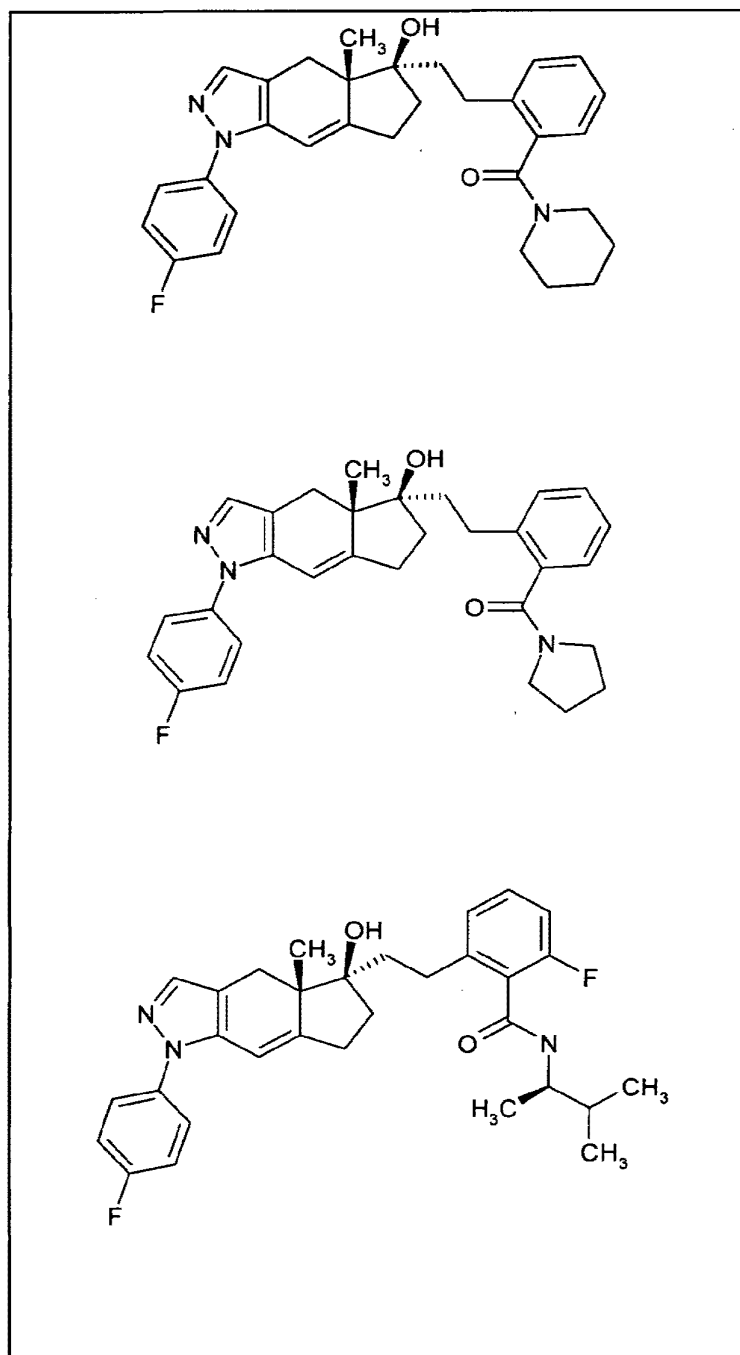


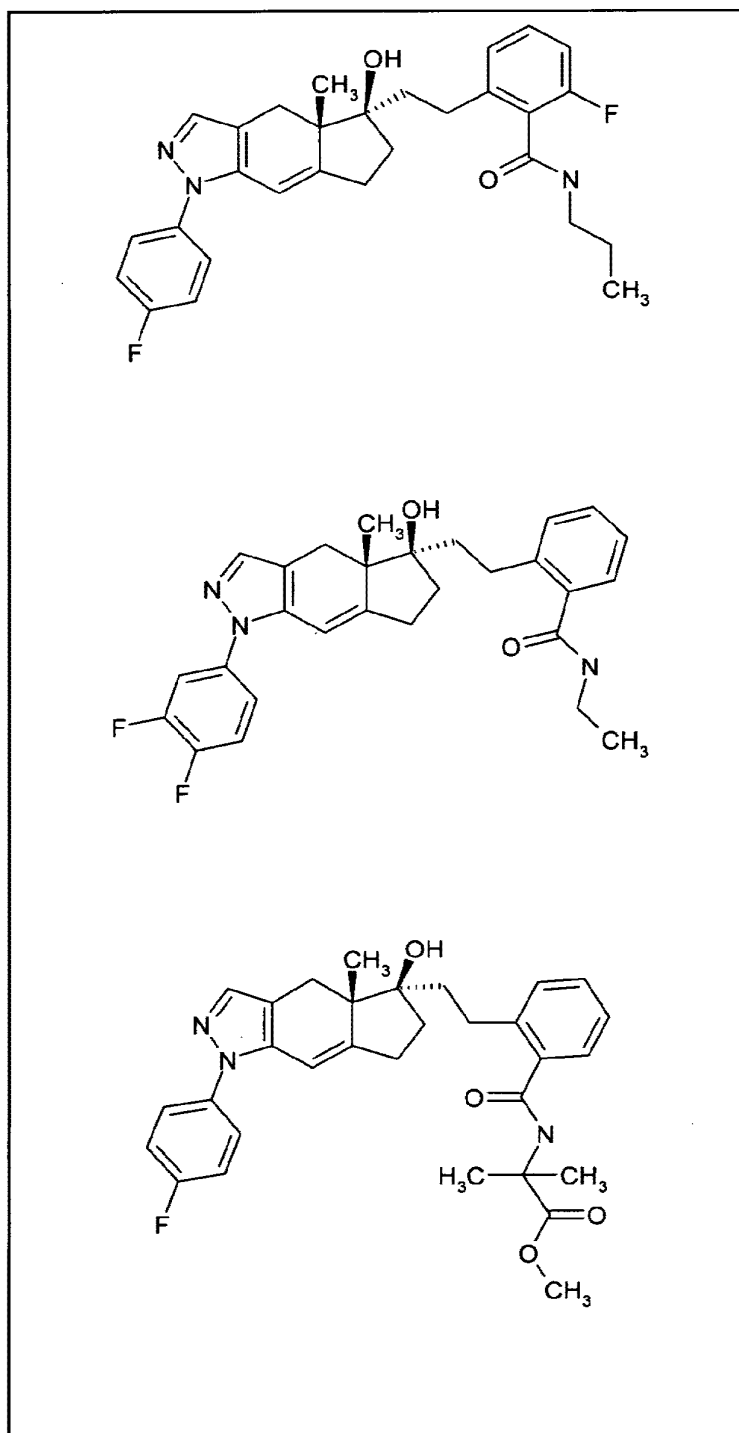


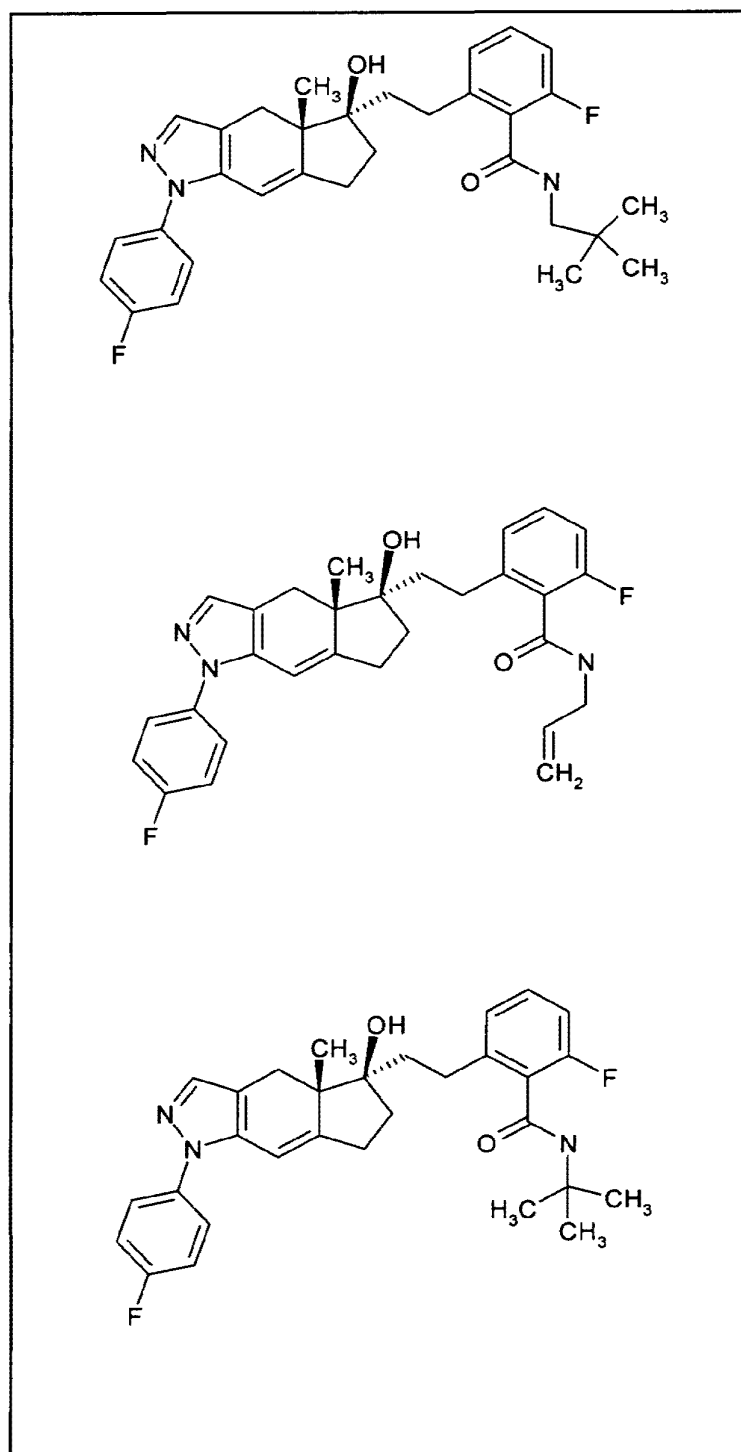


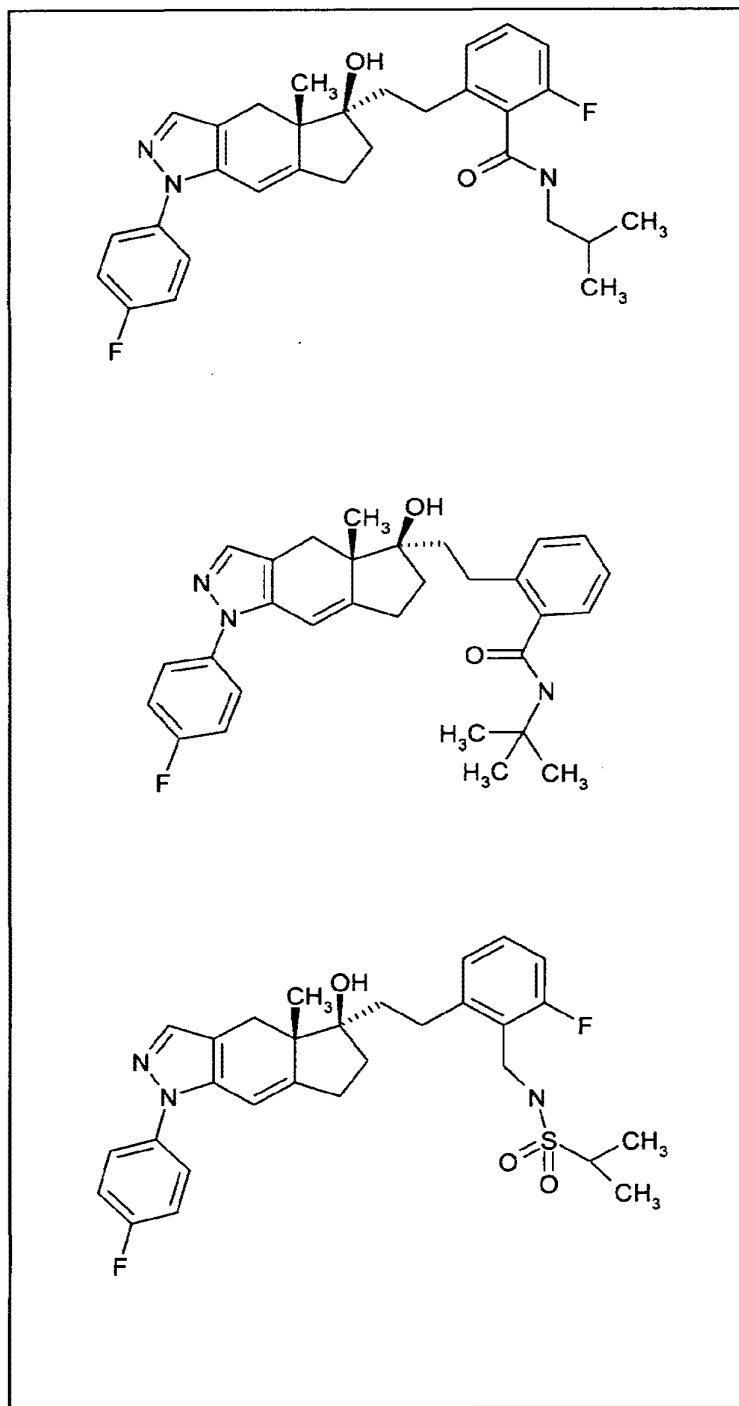


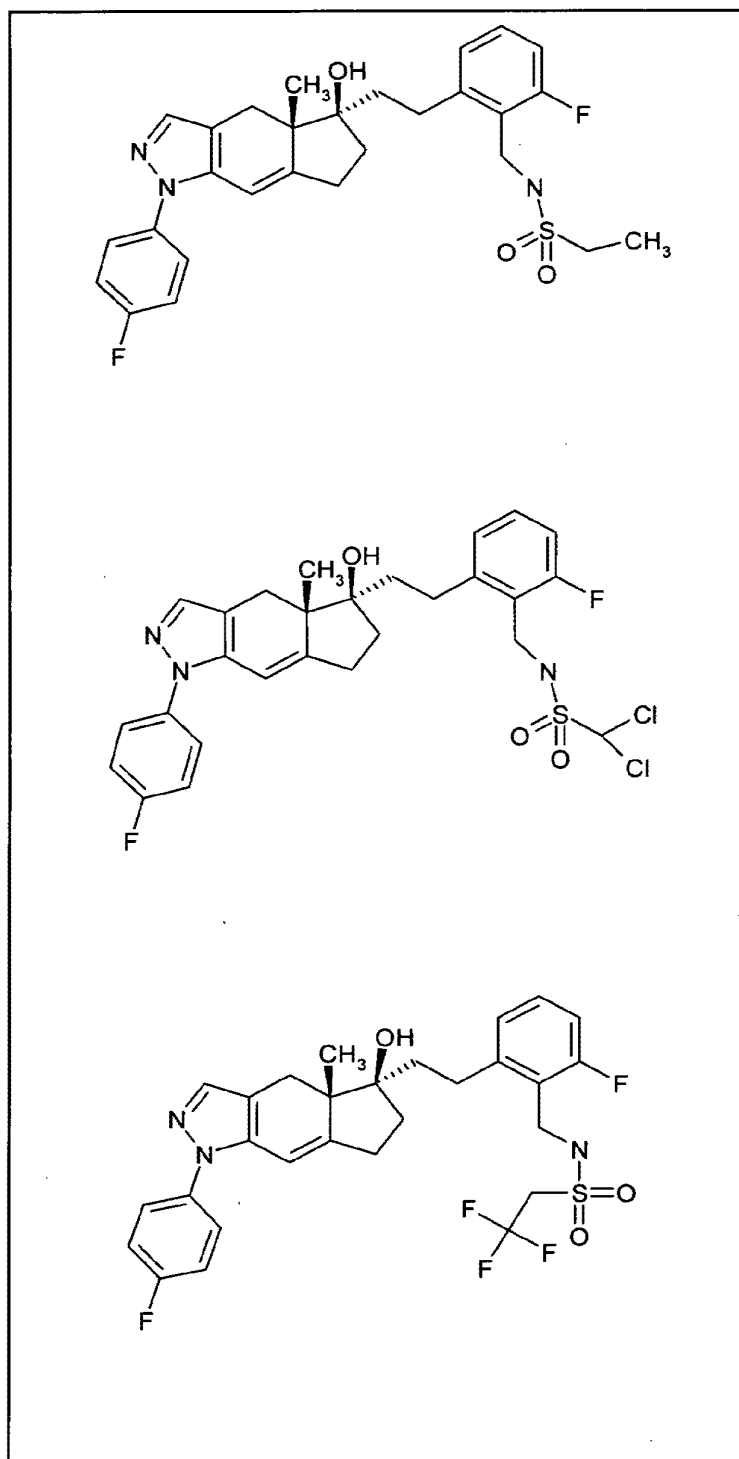


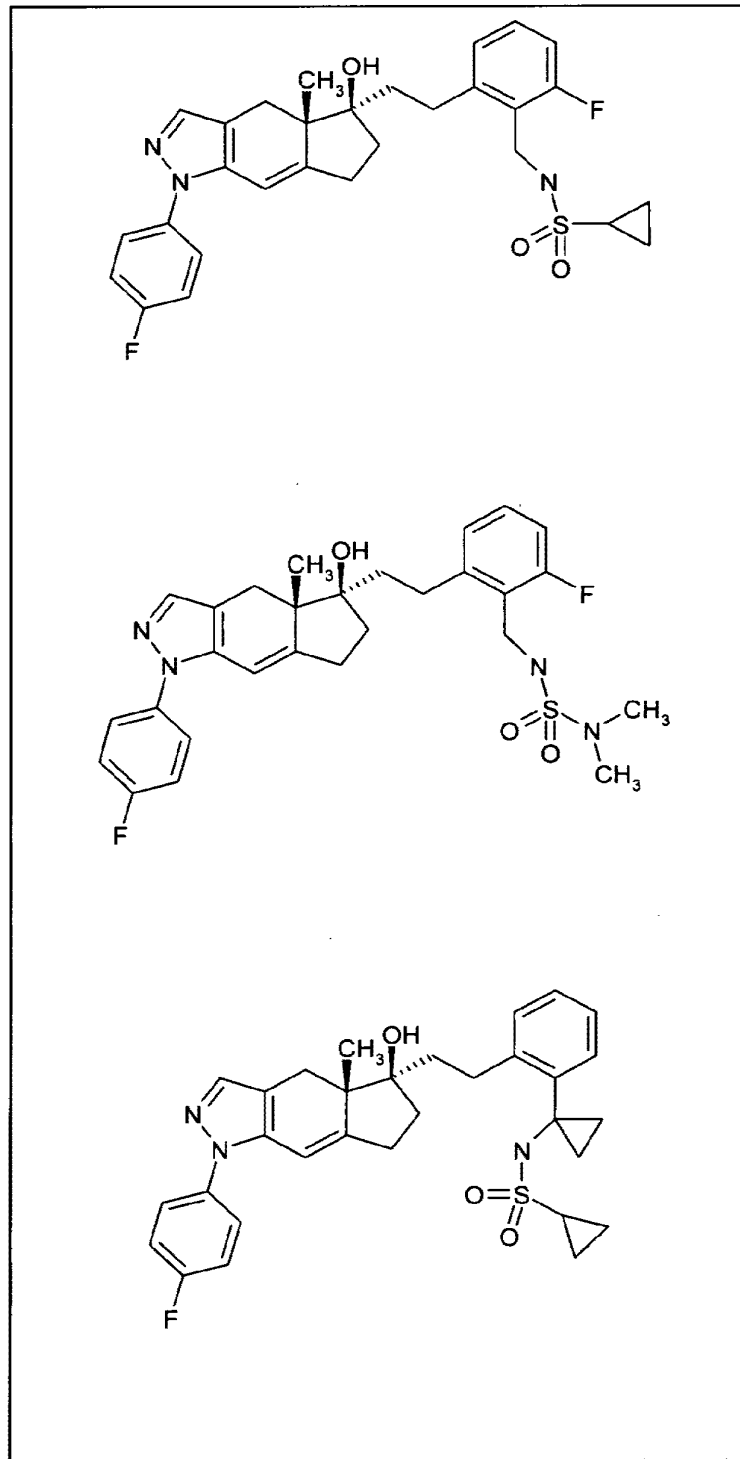


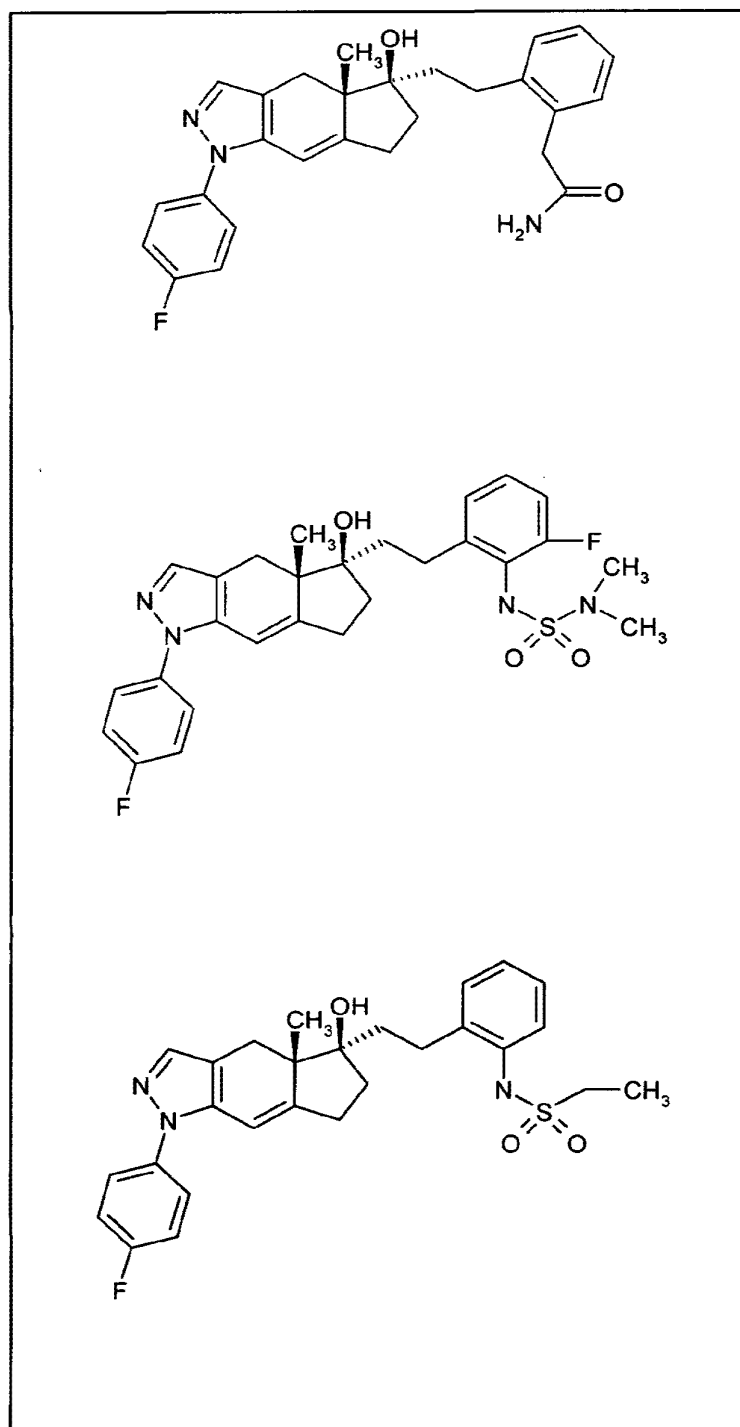


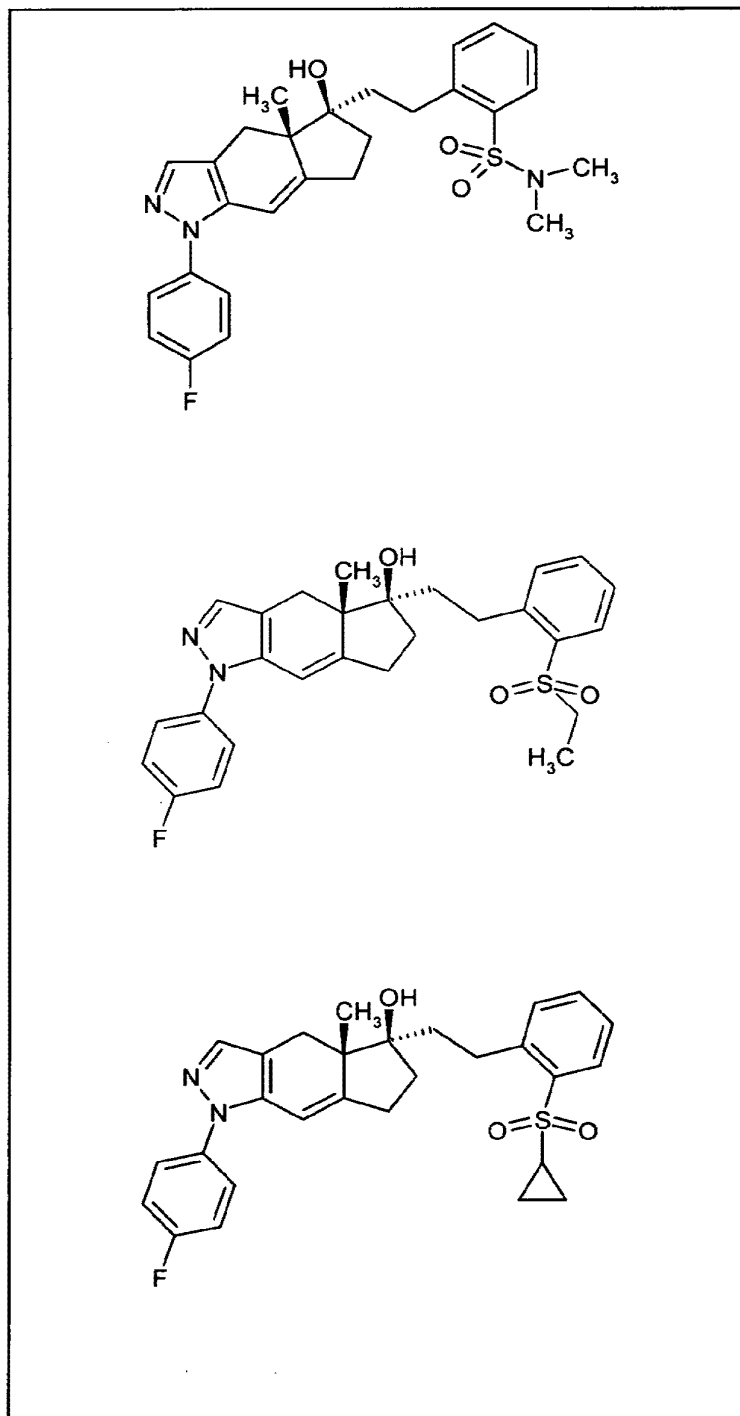


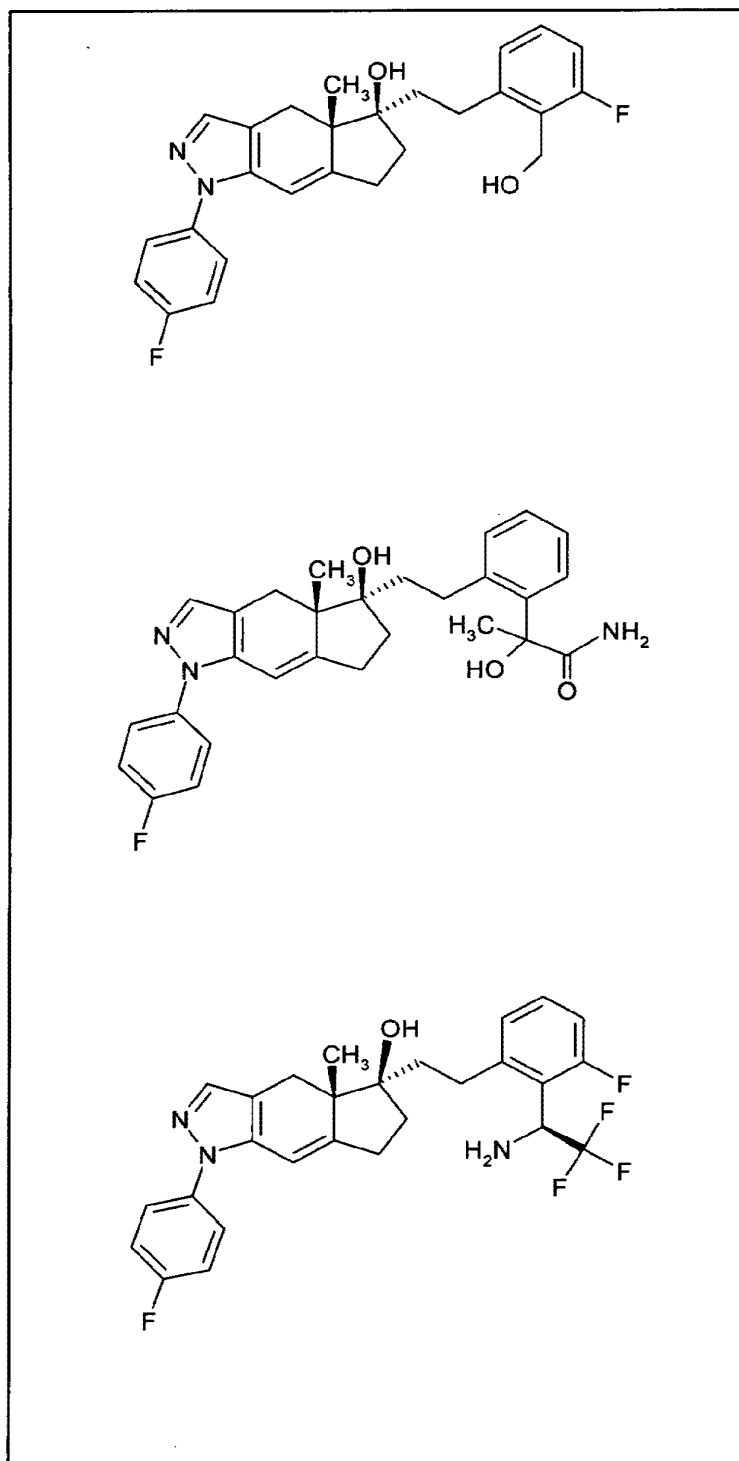


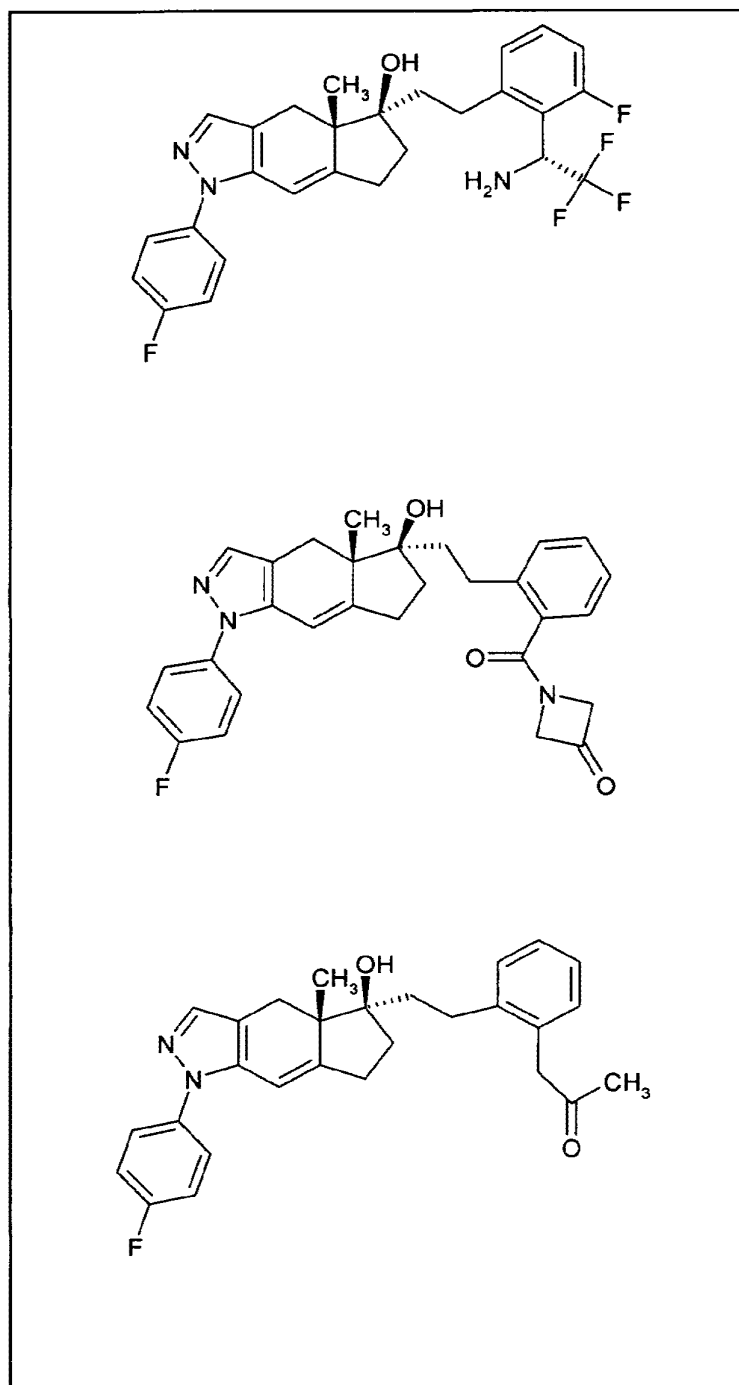


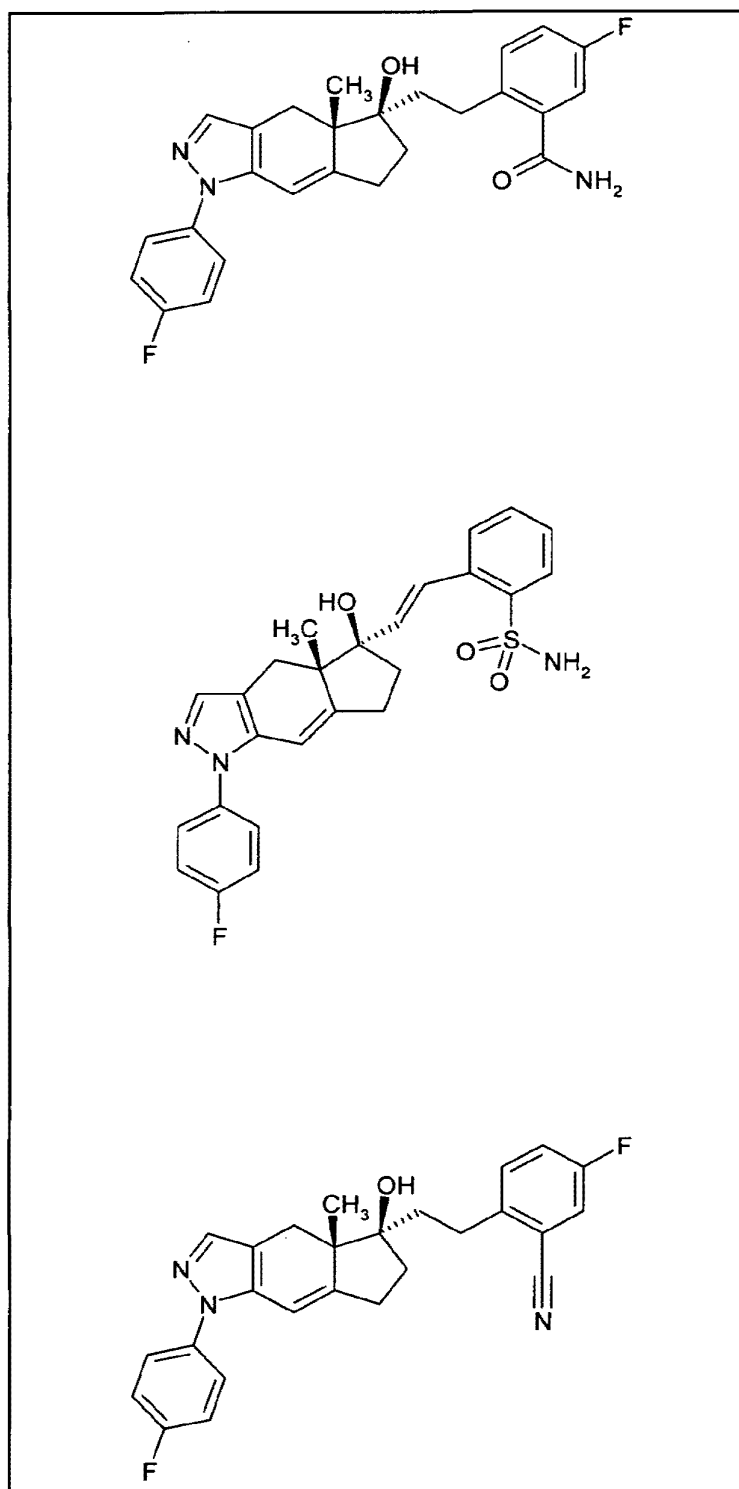


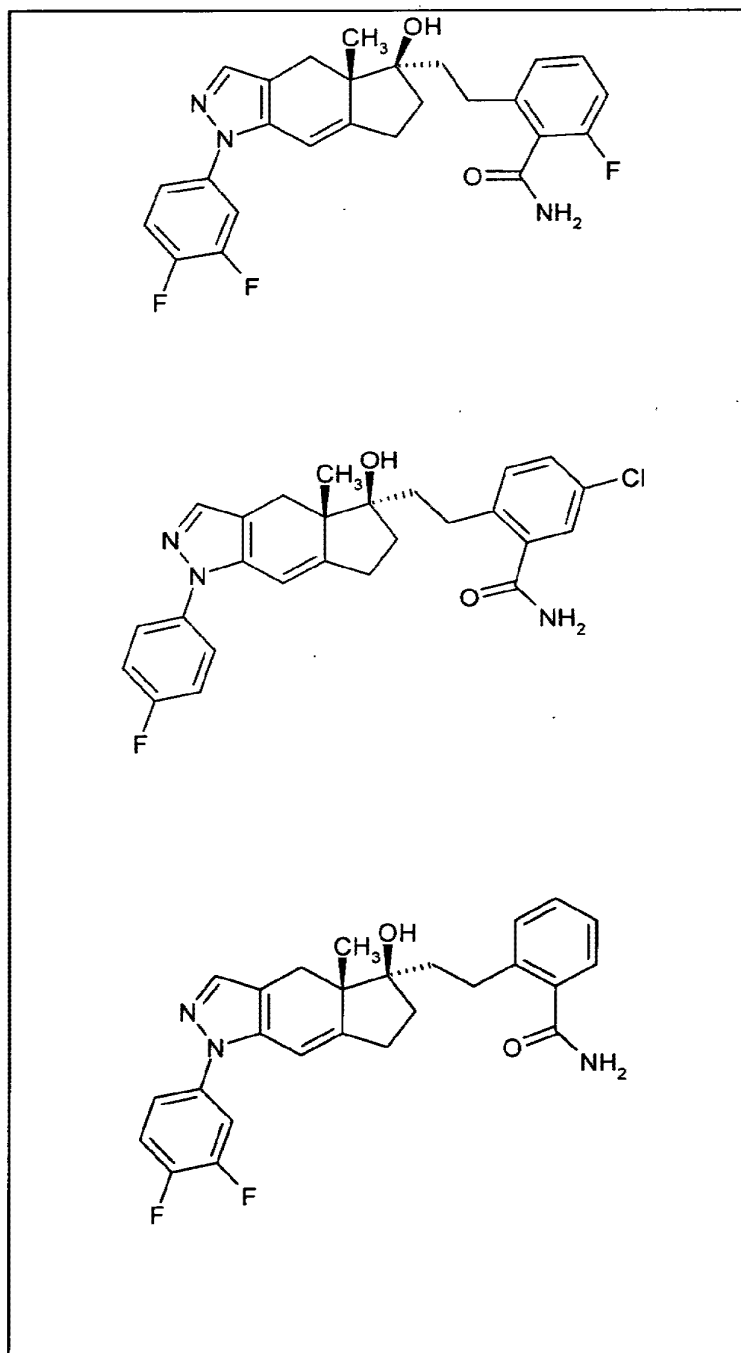


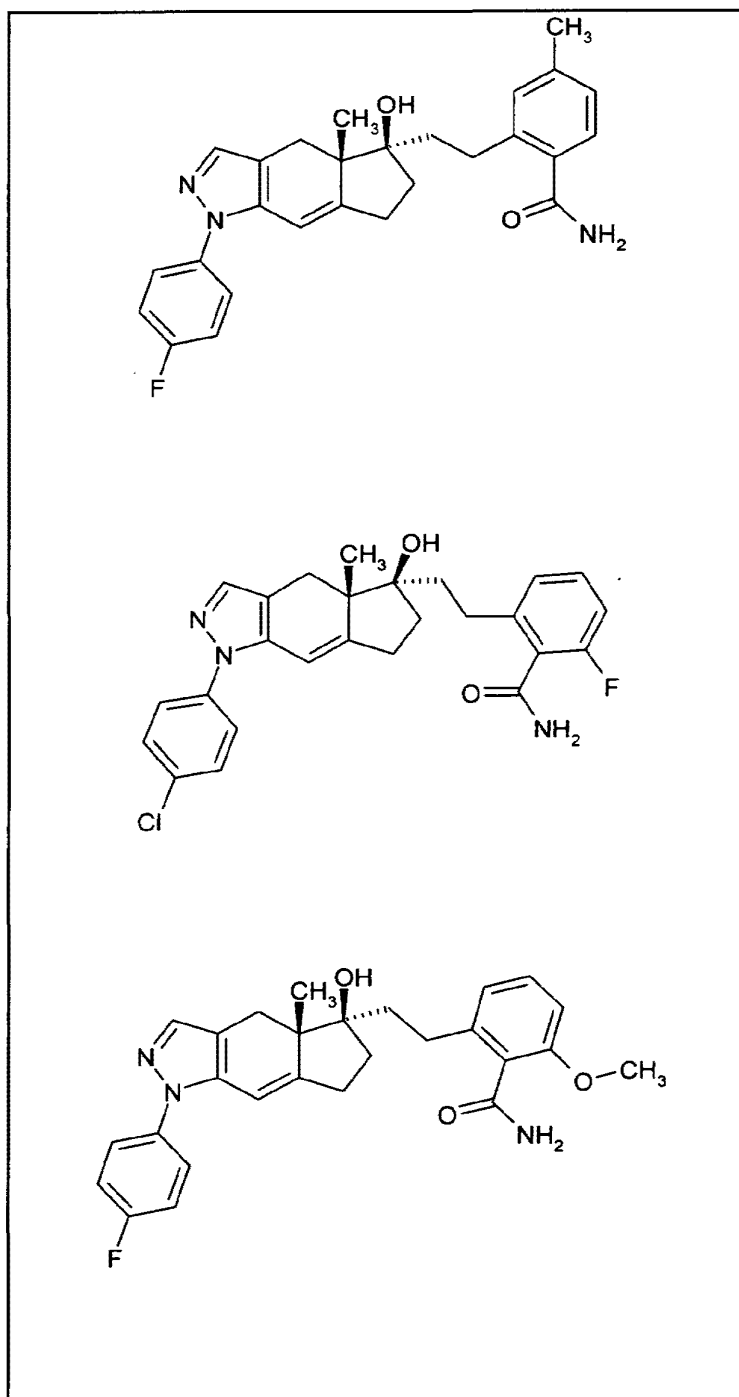


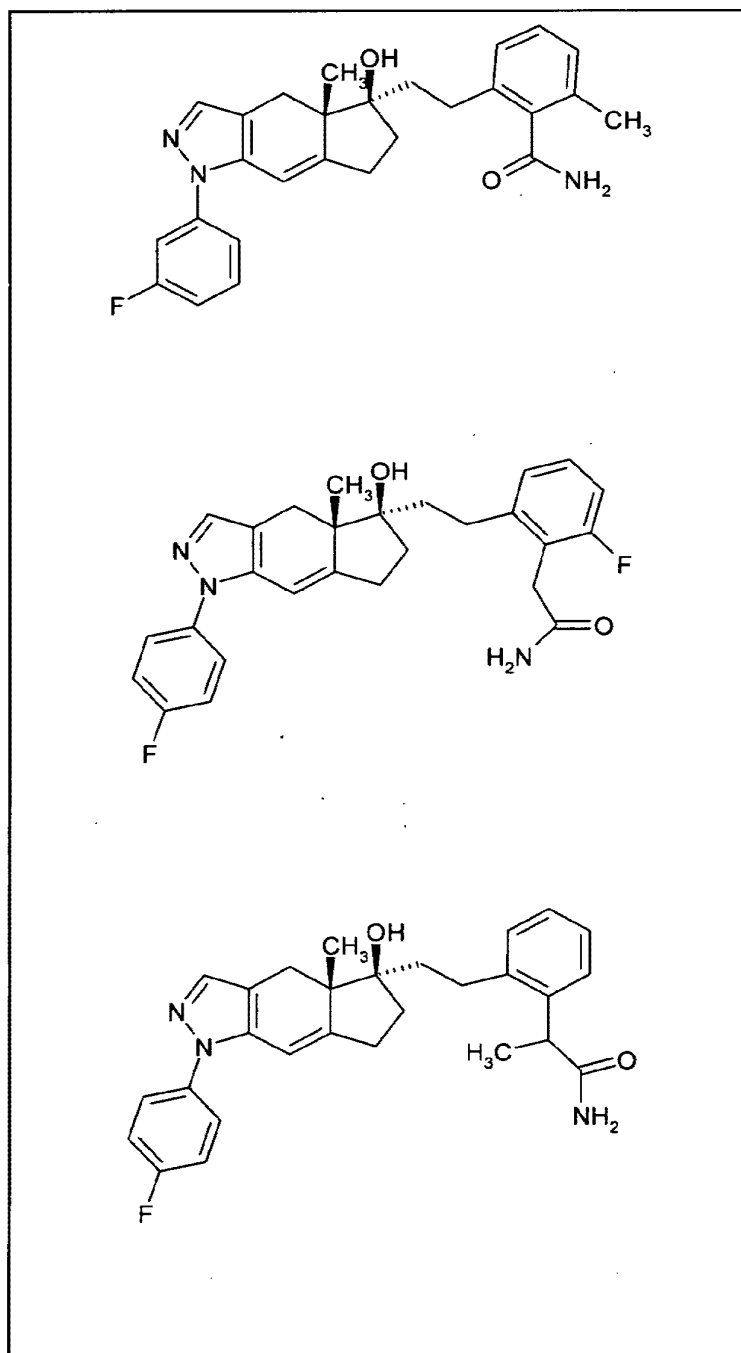


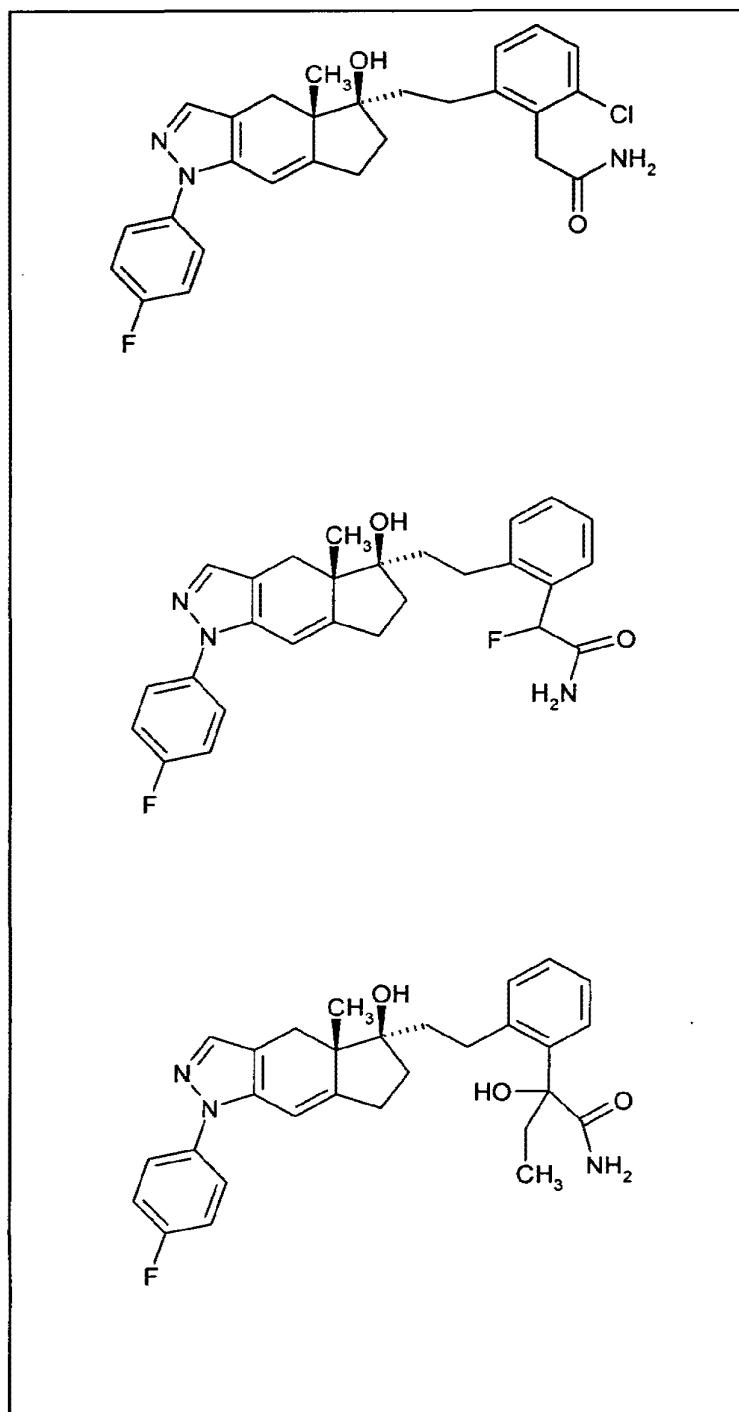


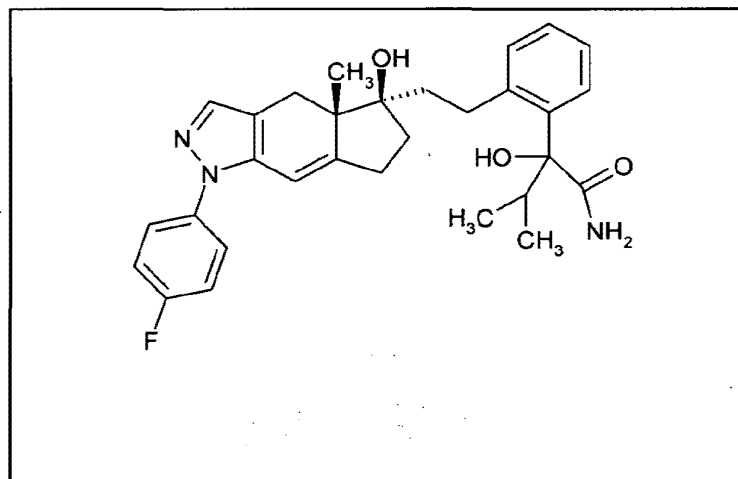












or a pharmaceutically acceptable salt of any of the foregoing compounds.

2. A pharmaceutical composition comprising a compound according to
5 Claim 1 in combination with a pharmaceutically acceptable carrier.
3. A method for treating a glucocorticoid receptor mediated disease or
condition in a mammalian patient in need of such treatment comprising administering the patient
a compound according to Claim 1 in an amount that is effective for treating the glucocorticoid
10 receptor mediated disease or condition.
4. The method according to Claim 3 wherein the glucocorticoid receptor
mediated disease or condition is selected from the group consisting of: tissue rejection,
leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal
15 hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of
myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation,
hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal
insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital
adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity, metabolic
20 syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa,
Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis,
uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary
disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic

active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, 5 inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer, Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, 10 depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

5. The method according to Claim 3 wherein the glucocorticoid receptor mediated disease or condition is selected from the group consisting of: tissue rejection, Cushing's 15 syndrome, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, hay fever, allergic rhinitis, asthma, organ transplantation, inflammatory scalp alopecia, psoriasis, discoid lupus erythematosus, and depression.

6. A method of selectively modulating the activation, repression, agonism 20 and antagonism effects of the glucocorticoid receptor in a mammal comprising administering to the mammal a compound according to Claim 1 in an amount that is effective to modulate the glucocorticoid receptor.

7. A method of partially or fully antagonizing, repressing, agonizing or 25 modulating the glucocorticoid receptor in a mammal comprising administering to the mammal an effective amount of compound according to Claim 1.

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(54) Title: A METHOD FOR TREATING CUSHING'S SYNDROME

(57) Abstract: The invention relates to a method for treating Cushing's syndrome in a patient, which method comprises administering the patient with a pharmaceutical composition comprising a glucocorticoid receptor antagonist, at least twice a day, or an extended-release composition of a glucocorticoid receptor antagonist, or a combination of a glucocorticoid receptor antagonist and an inhibitor of cortisol synthesis.

A method for treating Cushing's syndrome

5 The invention relates to a method for treating Cushing's syndrome using glucocorticoid receptor antagonists.

BACKGROUND OF THE INVENTION

10 Cushing's syndrome of endogenous origin is a hormonal disease with an estimated incidence of approximately 10 per 1 million persons (Meier and Biller, 1997). Cushing's syndrome is associated with an increased blood concentration of cortisol (hypercortisolism) or the presence in blood of glucocorticoid hormone excess over a long period of time. Cushing's syndrome is classified as either ACTH dependent or non ACTH dependent.

15 ACTH dependent Cushing's syndrome is characterised by a chronic ACTH hypersecretion which stimulates the growth of the adrenal glands and the hypersecretion of corticosteroids. The most common underlying cause of ACTH dependent Cushing's syndrome is excessive production of ACTH by pituitary adenomas known as Cushing's disease. Cushing's syndrome resulting from the production of ACTH in another location than the pituitary gland is known as ectopic
20 Cushing's syndrome. Examples of ectopic sites include thymoma, medullary carcinoma of the thyroid, pheochromocytoma, islet cell tumours of the pancreas and small cell carcinoma of the lung.

25 ACTH independent Cushing's syndromes are caused by adrenal tumors that can be either adenomas or carcinomas. Both adrenal adenomas and carcinomas are characterised by chronic cortisol hypersecretion.

30 Symptoms of Cushing's syndrome include a characteristic abnormal fat deposition around the neck, thinning of the skin, osteoporosis, moon face, weakness, fatigue, backache, headache, impotence, muscle atrophy, increased thirst, urination, insulin resistance, dyslipidemia, myopathy, amenorrhea, hypertension, weight gain, central obesity, steroid hypersecretion, elevated urinary cortisol excretion and mental status changes, in particular depression (Orth 1995; Dahia and Grossman, 1999).

Effective drug therapies for Cushing's syndrome currently are not satisfactory. The oral inhibitors of adrenal steroidogenesis are the most commonly used medical agents in

the treatment of Cushing's syndrome: these include metyrapone, ketoconazole, aminoglutethimide, mitotane and trilostane.

In ectopic ACTH secretion, when the tumor cannot be found or removed, medical therapy may be used to reduce cortisol production (Doppman et al, 1987, Doppman et al, 1989, Pass et al, 1990, Wajchenberg et al, 1994, Newell-Price et al, 1998).
5 Furthermore, clinical trials showed some efficacy using high-dose mifepristone once a day (Nieman et al, 1985; Chrousos et al, 1989; van der Lely, 1991, Newfield et al, 2000; Chu et al, 2001). A fractioned dosage of mifepristone was successfully given to a young child (Beaufrère et al, 1987).

10 However in a long term, such high dosage of mifepristone given with long intervals between doses (e.g. once a day) triggers a massive secretion of cortisol due to interruption of the endogenous feedback mechanism. This high level of cortisol then overwhelms the blockage of the glucocorticoid receptors, leading to hypercortisolism (Raux-Demay et al, 1990).

15

SUMMARY OF THE INVENTION

In order to avoid secretion of cortisol in response to the blockade of the glucocorticoid receptor, it is now proposed to give multiple low doses or a sustained-release low
20 dosage of glucocorticoid receptor antagonist, and/or to combine the glucocorticoid receptor antagonist with an inhibitor of cortisol synthesis, for treating Cushing's syndrome.

The invention thus provides a method for treating Cushing's syndrome in an adult or an
25 adolescent patient, which method comprises administering the patient with a pharmaceutical composition comprising a glucocorticoid receptor antagonist, at least twice a day.

The invention also relates to a glucocorticoid receptor antagonist for treating Cushing's
30 syndrome in an adult or an adolescent patient by administration of said glucocorticoid receptor antagonist at least twice a day.

The invention also provides a method for treating Cushing's syndrome in a patient,
which method comprises administering the patient with an extended-release
35 composition of a glucocorticoid receptor antagonist.

The invention also relates to an extended-release composition of a glucocorticoid receptor antagonist for treating Cushing's syndrome in an adult or an adolescent patient.

5

The invention further provides a method for treating Cushing's syndrome in a patient, which method comprises administering the patient with a glucocorticoid receptor antagonist and an inhibitor of cortisol synthesis.

10

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise indicated, the patient to be treated may be any human subject afflicted with Cushing's syndrome, whatever the sex and the age of the subject. The patient may be a child, an adolescent (i.e. generally a subject who is 12 years old or above), or an adult. The patient to be treated is afflicted with Cushing's syndrome, preferably caused by ectopic ACTH secretion.

In the context of the invention, the glucocorticoid receptor antagonist may be a steroidal or non-steroidal glucocorticoid receptor antagonist.

Examples of steroidal glucocorticoid receptor antagonists include, without limitation, mifepristone, cortexolone, dexamethasone-oxetane, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11-(4-dimethylaminoethoxyphenyl)-17-(propynyl)-17-(hydroxy-4,9-estradien-3-one, and 17-(hydroxy-17-(19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

In another preferred embodiment the steroidal glucocorticoid receptor is ulipristal, formerly known as CDB-2914, is 17 α -acetoxy-11 β -[4-N, N-dimethylamino-phenyl]-19-norpregna- 4, 9-diene-3, 20-dione, represented below.

It is a well-known steroid, more specifically a 19-norprogesterone, which possesses antiprogesterational and antiglucocorticoidal activity. This compound, and methods for its preparation, are described in U. S. Patent Nos. 4,954, 490,5, 073,548, and 5,929, 262, and international patent applications WO2004/065405 and WO2004/078709, all incorporated herein by reference.

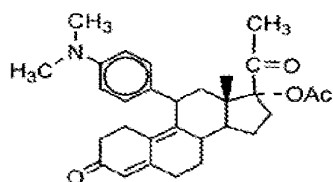
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Other steroidal glucocorticoid receptor antagonists include metabolites of CDB-2914, as described in Attardi et al, 2004 , e.g. monodemethylated CDB-2914 (CDB-3877) ;didemethylated CDB-2914 (CDB-3963) ; 17 α -hydroxy CDB-2914 (CDB-3236) ; aromatic A-ring derivative of CDB-2914 (CDB-4183).

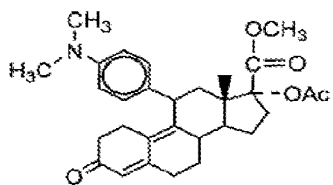
- 5 Still other steroidal glucocorticoid receptor antagonists include metabolites of mifepristone, as described in Attardi et al, 2004, e.g. monodemethylated mifepristone, didemethylated mifepristone, and 17- α -[3'-hydroxy-propynyl] mifepristone.

These steroidal glucocorticoid receptor antagonists, as well as other derivatives, are represented below.

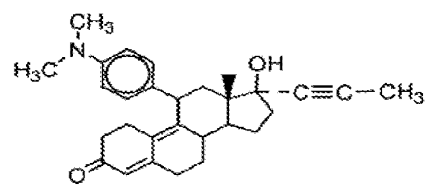
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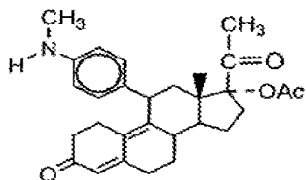
CDB-2914



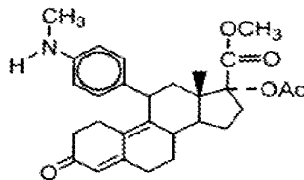
CDB-4124



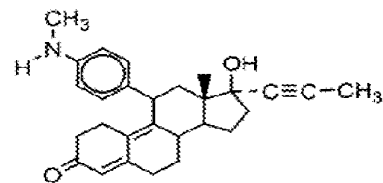
mifepristone



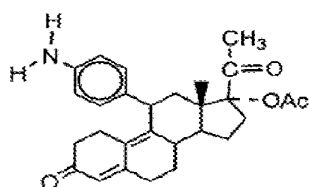
monodemethylated CDB-2914



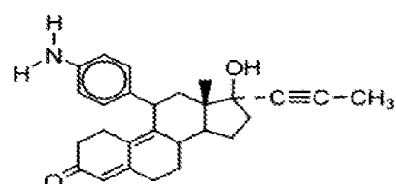
monodemethylated CDB-4124



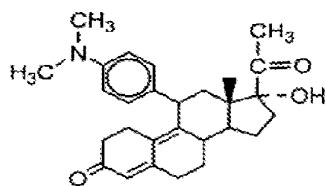
monodemethylated mifepristone



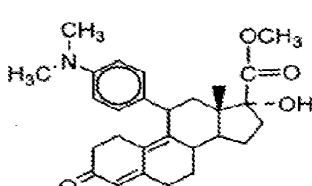
didemethylated CDB-2914



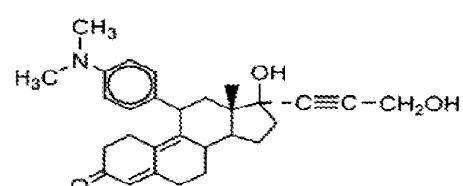
didemethylated mifepristone



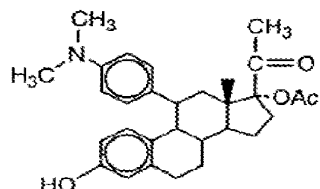
17α-hydroxy CDB-2914



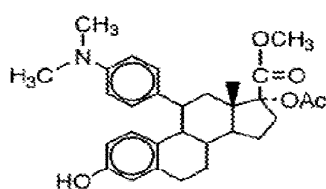
17α-hydroxy CDB-4124



17α-[3'-hydroxy-propynyl]
mifepristone



aromatic A-ring CDB-2914



aromatic A-ring CDB-4124

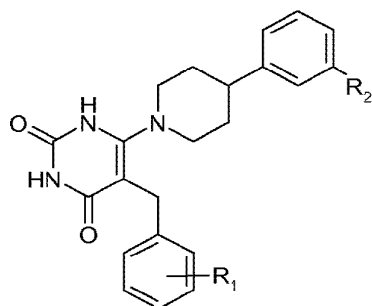
In a most preferred embodiment, the steroidal glucocorticoid receptor antagonist is mifepristone.

Examples of non-steroidal glucocorticoid receptor antagonists include, without limitation, N-(2-[4,4',4,4''-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4''-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4''-trichlorotrityl]imidazole); 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone;

5 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4''-trichlorotrityl)-1,2,4-triazole-3-thiol; 4.alpha.(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha.(R)-octahydro-phenanthrene-2,7-diol ("CP 394531") , 4.alpha. (S)-Benzyl-2(R)-prop-1-

10 ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-1-pyrrolidinyl]cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine and naloxone.

15 In another embodiment, the non-steroidal glucocorticoid antagonist is one of the series synthesized by Corcept therapeutics. WO2006/014394, incorporated herein by reference, reports the synthesis and biological characterization of 48 novel 5,6-substituted pyrimidine-2,4-dione GR modulators. The most active compounds are compounds of formula I



20 (I)

wherein

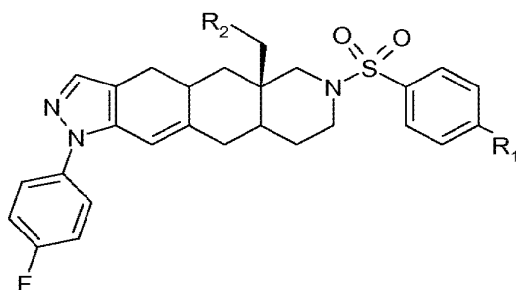
R₁ is H and R₂ is H or Cl,

or R₁ is o-chloro or m-chloro and R₂ is H.

In WO05/087769, incorporated herein by reference, Corcept therapeutics described the

25 synthesis and biological testing of 150 compounds with a tetracyclic core ring structure that they term as azadecalins. Preferred azadecalin antagonists are compounds of formula II

(II)



wherein

R1 is F and R2 is pyrrolidine,

or R1 is t-butyl and R2 is selected from the group consisting of H, a phenyl group, and -

5 CH₂-O-CH₃

The compounds may be in the form of pharmaceutically acceptable salts, esters, optically active isomers, racemates or hydrates.

10 *Multiple doses*

In a preferred embodiment, the invention provides a method for treating Cushing's syndrome in an adult or an adolescent patient, which method comprises administering the patient with a pharmaceutical composition comprising a glucocorticoid receptor antagonist, at least twice a day.

15 Most preferably, the patient is administered with pharmaceutical composition comprising a glucocorticoid receptor antagonist at least three times a day, e.g. three or four times a day.

Such chronic daily administration of the glucocorticoid receptor antagonist in subjects with Cushing's syndrome makes it possible to normalize glucocorticoid-dependent parameters through its cortisol-blocking action.

20 Preferably the daily dosage is less than about 40mg/kg/day, preferably less than about 20mg/kg/day.

The total daily amount of the glucocorticoid receptor antagonist administered may be advantageously inferior or equal to 800mg, preferably inferior or equal to 600mg, still preferably inferior or equal to 400mg, still more preferably inferior or equal to 300mg.

25 The composition may be administered by any convenient route. The active ingredient may be administered by any convenient route, including oral, buccal, parenteral, transdermal, vaginal, uterine, rectal, nasal etc. Preferably the pharmaceutical composition is suitable for oral or parenteral administration. In a particular embodiment, 30 the composition is in the form of an infusion to the patient.

Extended-release form:

In another embodiment, the invention provides a method for treating Cushing's syndrome in a patient, which method comprises administering the patient with an
5 extended-release composition of a glucocorticoid receptor antagonist.

By `extended- release` is meant that the active ingredient is released from the formulation and thus made available for absorption by the body in a sustained manner, this being determined by the release rate controlling substance and interactions
10 between the active ingredient, the release rate controlling substance and the media surrounding the formulation (e.g gastric juice).

Preferably the daily dosage is less than about 40mg/kg/day, preferably less than about 20mg/kg/day.

The total daily amount of the glucocorticoid receptor antagonist administered may be advantageously inferior or equal to 800mg, preferably inferior or equal to 600mg, still
15 preferably inferior or equal to 400mg, still more preferably inferior or equal to 300mg.

The composition may be administered by any convenient route. The active ingredient may be administered by any convenient route, including oral, buccal, parenteral, transdermal, vaginal, intra-uterine, rectal, nasal, etc. Preferably the pharmaceutical composition is suitable for oral or parenteral administration. In a particular embodiment,
20 the extended-release composition is suitable for intradermal administration. For instance, the extended-release composition may be in the form of a patch or an implant. In still another embodiment, the extended-release composition is suitable for intra-uterine administration.

25 *Association with an inhibitor of cortisol synthesis:*

The invention further provides a method for treating Cushing's syndrome in a patient, which method comprises administering the patient with a glucocorticoid receptor antagonist and an inhibitor of cortisol synthesis.

In a preferred embodiment, the inhibitor of cortisol synthesis is an adrenolytic agent.
30 Preferably, the inhibitor of cortisol synthesis is mitotane. In another preferred embodiment, the inhibitor of cortisol synthesis is metyrapone.

Other examples of inhibitors of cortisol synthesis include, without limitation, aminoglutethimide, sodium valproate, an enkephalin, an opioid, clonidine, oxytocin, etomidate, trilostane, phenytoin, procaine, vitamin C, a salicylate, cimetidine, and

lidocaine, as well as ketoconazole, clotrimazole; N-(triphenylmethyl)imidazole; N-([2-fluoro-9-phenyl]fluorenyl) imidazole; and N-([2-pyridyl]diphenylmethyl)imidazole.

Preferably the glucocorticoid receptor antagonist is mifepristone and the inhibitor of cortisol synthesis is mitotane, metyrapone, aminoglutethimide, fluconazole or
5 ketoconazole.

Preferably the daily dosage is less than about 40mg/kg/day, preferably less than about 20mg/kg/day.

The total daily amount of the glucocorticoid receptor antagonist administered may be advantageously inferior or equal to 800mg, preferably inferior or equal to 600mg, still
10 preferably inferior or equal to 400mg, still more preferably inferior or equal to 300mg.

The composition may be administered by any convenient route. The active ingredients may be administered by any convenient route, including oral, buccal, parenteral, transdermal, vaginal, uterine, rectal, nasal, etc. Preferably the pharmaceutical composition is suitable for oral or parenteral administration. In a particular embodiment,
15 the composition is in the form of an infusion to the patient.

Routes of administration:

For a brief review of present methods for drug delivery, see, Langer, Science
20 249:1527-1533 (1990), which is incorporated herein by reference. Methods for preparing administrable compounds are known or are apparent to those skilled in the art and are described in more detail in, for example, Remington's Pharmaceutical Science, 17th ed., Mack Publishing Company, Easton, Pa. (1985), which is incorporated herein by reference, and which is hereinafter referred to as "Remington."

25 For solid compositions, conventional non toxic solid carriers may be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic
30 composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed.

Oral solid dosage forms are preferentially compressed tablets or capsules. Compressed tablets may contain any of the excipients described above which are
35 diluents to increase the bulk of the active ingredient so that production of a compressed

tablet of practical size is possible. Binders, which are agents which impart cohesive qualities to powdered materials are also necessary. Starch, gelatine, sugars such as lactose or dextrose, and natural and synthetic gums are used. Disintegrants are necessary in the tablets to facilitate break-up of the tablet. Disintegrants include
5 starches, clays, celluloses, algins, gums and crosslinked polymers. Lastly small amounts of materials known as lubricants and glidants are included in the tablets to prevent adhesion to the tablet material to surfaces in the manufacturing process and to improve the flow characteristics of the powder material during manufacture. Colloidal silicon dioxide is most commonly used as a glidant and compounds such as talc or
10 stearic acids are most commonly used as lubricants. Procedures for the production and manufacture of compressed tablets are well known by those skilled in the art (See Remington).

Capsules are solid dosage forms using preferentially either a hard or soft gelatine shell
15 as a container for the mixture of the active ingredient and inert ingredients. Procedures for production and manufacture of hard gelatin and soft elastic capsules are well known in the art (See Remington).

Buccal forms or devices are also useful, such as those described in U.S. patent
20 application 20050208129, herein incorporated by reference. U.S. patent application 20050208129 describes a prolonged release bioadhesive mucosal therapeutic system containing at least one active principle, with an active principle dissolution test of more than 70% over 8 hours and to a method for its preparation. Said bioadhesive therapeutic system comprises quantities of natural proteins representing at least 50%
25 by weight of active principle and at least 20% by weight of said tablet, between 10% and 20% of an hydrophilic polymer, and compression excipients, and comprising between 4% and 10% of an alkali metal alkylsulphate to reinforce the local availability of active principle and between 0.1% and 1% of a monohydrate sugar.

For parenteral administration, fluid unit dosage forms are prepared utilizing the
30 compounds and a sterile vehicle, water being preferred. The active ingredient, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filtered sterilized before filling into a suitable vial or ampoule and
35 sealing. Advantageously, adjuvants such as a local anesthetic, preservative and

buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the liquid prior to use. Parenteral
5 suspensions can be prepared in substantially the same manner except that the compounds are suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the
10 active ingredient.

Additionally, a suppository can be employed to deliver the active ingredient. The active compound can be incorporated into any of the known suppository bases by methods known in the art. Examples of such bases include cocoa butter, polyethylene glycols
15 (carbowaxes), polyethylene sorbitan monostearate, and mixtures of these with other compatible materials to modify the melting point or dissolution rate. These suppositories can weigh from about 1 to 2.5 gm.

Transdermal delivery systems comprising a penetration enhancer and an occlusive
20 backing are of use to deliver the active ingredient. Examples of penetration enhancers include dimethyl sulfoxide, dimethyl acetamide and dimethylformamide.

Systems comprising polymeric devices which slowly release or slowly erode and release within the body to provide continuous supplies of the active ingredient are also
25 of use.

The below example illustrates the invention without limiting its scope.

EXAMPLE:

30 **Case-study:**

A 53 year-old female subject, first presented with clinical symptoms of Cushing's syndrome in August 2006, and she was diagnosed with Cushing's syndrome secondary to ectopic ACTH secretion in March 2007. She received 200mg mifepristone, three times a day (in the morning, at noon, and in the evening) for 2.5
35 weeks before dose reduction for 1 week to 400 mg (200 mg twice a day).

The administration of mifepristone rapidly improved (after 2 weeks of treatment) general clinical consequences of hypercortisolism: glycemia returned to normal, insulin was stopped and dose of metformin decreased by two. The dose of enalapril previously administered for hypertension was decreased from 30mg to 10 mg.

5

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- 5
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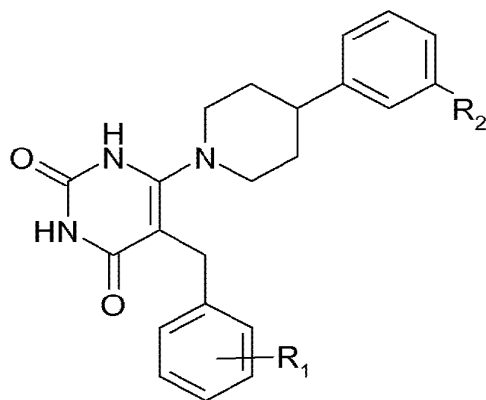
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CLAIMS

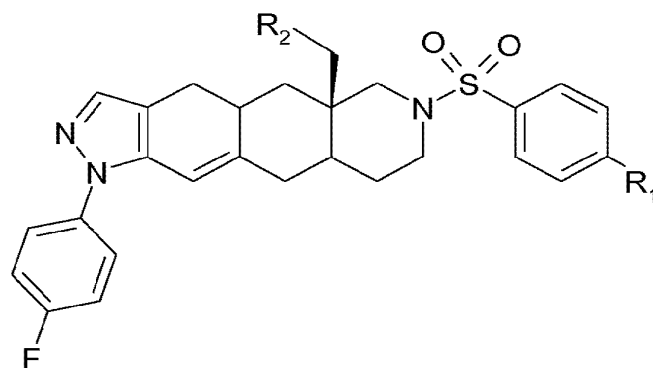
1. A method for treating Cushing's syndrome in an adult or an adolescent patient, which method comprises administering the patient with a pharmaceutical composition comprising a glucocorticoid receptor antagonist, at least twice a day.
5
2. The method of claim 1, wherein the patient is administered with pharmaceutical composition comprising a glucocorticoid receptor antagonist at least three times a day.
10
3. The method of claim 1, wherein the total daily amount of the glucocorticoid receptor antagonist administered is preferably less than about 20mg/kg/day
4. The method of claim 1, wherein the total daily amount of the glucocorticoid receptor antagonist administered is inferior or equal to 800mg
15
5. The method of claim 4, wherein the total daily of the glucocorticoid receptor antagonist administered is inferior or equal to 600mg.
20
6. The method of claim 1, wherein the glucocorticoid receptor antagonist is a steroidal glucocorticoid receptor antagonist.
7. The method of claim 6, wherein the steroidal glucocorticoid receptor antagonist is selected from the group consisting of mifepristone, monodemethylated mifepristone, didemethylated mifepristone, 17- α -[3'-hydroxy-propynyl] mifepristone, ulipristal (CDB-2914), CDB-3877, CDB-3963, CDB-3236, CDB-4183, cortexolone, dexamethasone-oxetane, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11-(4-dimethylaminoethoxyphenyl)-17-(propynyl)-17-(hydroxy-4,9-estradien-3-one, and 17-(hydroxy-17-(19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.
25
30
8. The method of claim 7, wherein the steroidal glucocorticoid receptor antagonist is mifepristone.
35

9. The method of claim 1, wherein the glucocorticoid receptor antagonist is a non-steroidal glucocorticoid receptor antagonist.

10. The method of claim 9, wherein the non-steroidal glucocorticoid receptor antagonist is selected from the group consisting of N-(2-[4,4',4''-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4''-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4''-trichlorotrityl]imidazole); 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4''-trichlorotrityl)-1,2,4-triazole-3-thiol; 4.alpha.(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP 394531"), 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidiny)cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine, naloxone compounds of formula I
(I)



20 wherein
R1 is H and R2 is H or Cl,
or R1 is o-chloro or m-chloro and R2 is H.
or compounds of formula II
(II)



wherein

R₁ is F and R₂ is pyrrolidine,

or R₁ is t-butyl and R₂ is selected from the group consisting of H, a phenyl
 5 group, and -CH₂-O-CH₃

11. The method of claim 1, wherein the pharmaceutical composition is suitable for
 oral administration.

10 12. The method of claim 1, wherein the pharmaceutical composition is suitable for
 parenteral administration.

13. The method of claim 1, wherein the composition is in the form of an infusion to
 the patient.

15

14. The method of claim 1, wherein the composition is suitable for buccal,
 intradermal and nasal administration.

15. A method for treating Cushing's syndrome in a patient, which method
 20 comprises administering the patient with an extended-release composition of a
 glucocorticoid receptor antagonist.

16. The method of claim 15, wherein the glucocorticoid receptor antagonist is a
 steroidal glucocorticoid receptor antagonist.

25

17. The method of claim 16, wherein the steroidal glucocorticoid receptor
 antagonist is selected from the group consisting of mifepristone,
 monodemethylated mifepristone, didemethylated mifepristone, 17- α -[3'-

hydroxy-propynyl] mifepristone, ulipristal, CDB-3877, CDB-3963, CDB-3236, CDB-4183, cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11(-(4-dimethylaminoethoxyphenyl)-17(-propynyl)-17(-hydroxy-4,9-estradien-3one, and 17(-hydroxy-17(-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

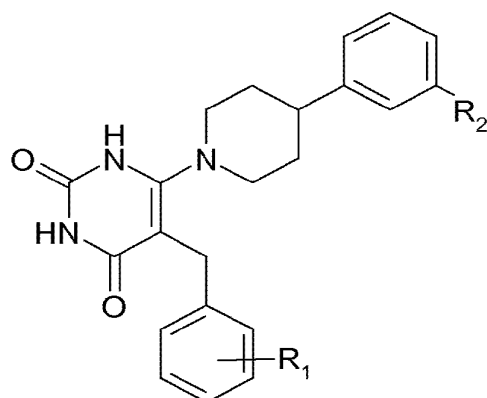
18. The method of claim 16, wherein the steroidal glucocorticoid receptor antagonist is mifepristone.

10

19. The method of claim 15, wherein the glucocorticoid receptor antagonist is a non-steroidal glucocorticoid receptor antagonist.

20. The method of claim 19, wherein the non-steroidal glucocorticoid receptor antagonist is selected from the group consisting of N-(2-[4,4',441 -trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4"]-trichlorotrityl)imidazole; 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4"-trichlorotrityl)-1,2,4-triazole-3-thiol; 4.alpha.(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP 394531") , 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-1 pyrrolidinyl]cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine, naloxone and compounds of formula I (I)

25



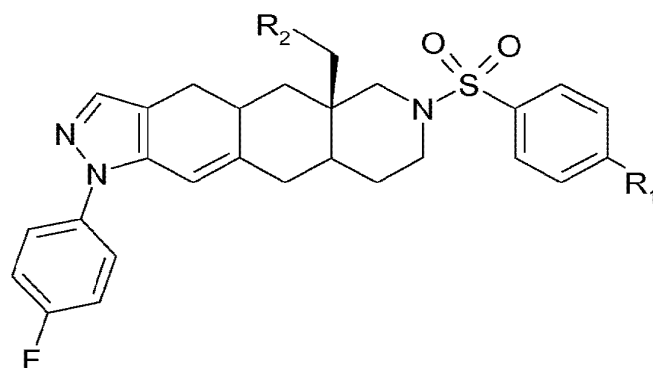
wherein

R1 is H and R2 is H or Cl,

or R1 is o-chloro or m-chloro and R2 is H.

5 or compounds of formula II

(II)



wherein

R1 is F and R2 is pyrrolidine, or R1 is t-butyl and R2 is selected from the group
 10 consisting of H, a phenyl group, and $-\text{CH}_2-\text{O}-\text{CH}_3$.

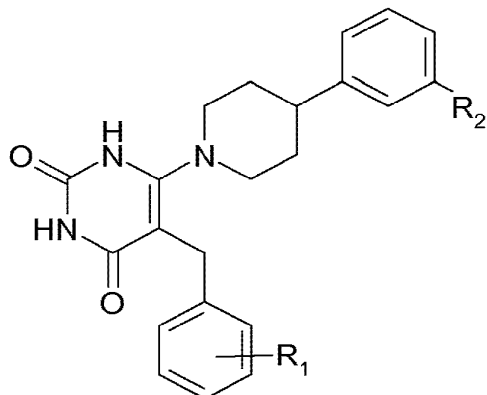
21. The method of claim 15, wherein the extended-release composition is suitable
 for oral administration.

15 22. The method of claim 15, wherein the extended-release composition is suitable
 for parenteral administration.

23. The method of claim 15, wherein the extended-release composition is suitable
 for intradermal administration.

24. The method of claim 23, wherein the extended-release composition is in the form of a transdermal.
- 5 25. The method of claim 24, wherein the extended-release composition is in the form of a patch.
26. The method of claim 24, wherein the extended-release composition is in the form of an implant.
- 10 27. The method of claim 15, wherein the extended-release composition is suitable for intra-uterine administration.
28. A method for treating Cushing's syndrome in a patient, which method
15 comprises administering the patient with a glucocorticoid receptor antagonist and an inhibitor of cortisol synthesis.
29. The method of claim 28, wherein the glucocorticoid receptor antagonist is a steroidal glucocorticoid receptor antagonist.
- 20 30. The method of claim 29, wherein the steroidal glucocorticoid receptor antagonist is selected from the group consisting of mifepristone, , monodemethylated mifepristone, didemethylated mifepristone, 17- α -[3'-hydroxy-propynyl] mifepristone, ulipristal, CDB-3877, CDB-3963, CDB-3236,
25 CDB-4183, cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11-(4-dimethylaminoethoxyphenyl)-17-(propynyl)-17-(hydroxy-4,9-estradien-3-one, and 17-(hydroxy-17-(19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.
- 30 31. The method of claim 30, wherein the steroidal glucocorticoid receptor antagonist is mifepristone.
32. The method of claim 28, wherein the glucocorticoid receptor antagonist is a
35 non-steroidal glucocorticoid receptor antagonist.

33. The method of claim 32, wherein the non-steroidal glucocorticoid receptor antagonist is selected from the group consisting of N-(2-[4,4',4,4'-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-(4,4',4"-trichlorotrityl)imidazole; 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4"-trichlorotrityl)-1,2,4-triazole-3-thiol; 4.alpha.(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP 394531"), 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide, breamazocine, ethylketocyclazocine, naloxone and compounds of formula I



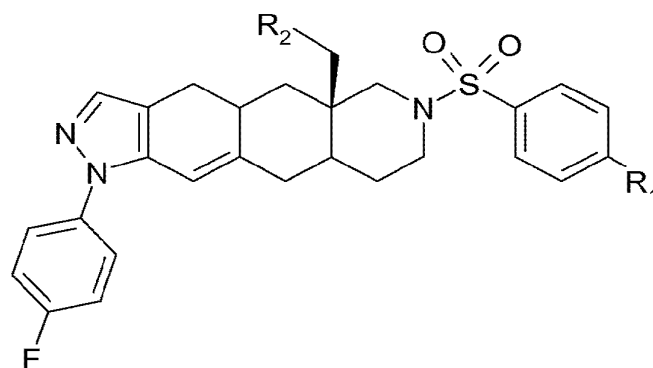
(I)

wherein

R₁ is H and R₂ is H or Cl,or R₁ is o-chloro or m-chloro and R₂ is H.

or compounds of formula II

(II)



wherein

R1 is F and R2 is pyrrolidine,

or R1 is t-butyl and R2 is selected from the group consisting of H, a phenyl
 5 group, and $-\text{CH}_2-\text{O}-\text{CH}_3$.

34. The method of claim 28, wherein the inhibitor of cortisol synthesis is an
 adrenolytic agent.

10 35. The method of claim 34, wherein the inhibitor of cortisol synthesis is mitotane.

36. The method of claim 28, wherein the inhibitor of cortisol synthesis is
 metyrapone.

15 37. The method of claim 28, wherein the inhibitor of cortisol synthesis is selected
 from the group consisting of aminoglutethimide, sodium valporate, an
 enkephalin, an opioid, clonidine, oxytocin, etomidate, trilostane, phenytoin,
 procaine, vitamin C, a salicylate, cimetidine, and lidocaine

20 38. The method of claim 28, wherein the inhibitor of cortisol synthesis is selected
 from the group consisting of ketoconazole, clotrimazole; N-
 (triphenylmethyl)imidazole; N-([2-fluoro-9-phenyl]fluorenyl)imidazole; and N-([2-
 pyridyl]diphenylmethyl)imidazole, whatever the pharmaceutical form is.

25

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: MAO, YIFAN KILPATRICK TOWNSEND & STOCKTON LLP MAILSTOP: IP DOCKETING - 22 1100 PEACHTREE STREET, SUITE 2809 ATLANTA GA 30309 USA	<h1 style="margin: 0;">PCT</h1> <p style="margin: 0;">NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION</p> <p style="margin: 0;">(PCT Rule 44.1)</p>
	Date of mailing <i>(day/month/year)</i> 20 April 2017 (20.04.2017)
Applicant's or agent's file reference 1036009	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2017/013974	International filing date <i>(day/month/year)</i> 18 January 2017 (18.01.2017)
Applicant CORCEPT THERAPEUTICS, INC.	

1. The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
- Filing of amendments and statement under Article 19:**
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
- When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
- How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70
- For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9-011.**
2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders



The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the international Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, within **20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months** from the priority date, the applicant may request that a supplementary international search be carried out by an International Searching Authority, that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

APR 27 PM 11:24

Name and mailing address of the ISA/KR International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea  Facsimile No. 82-42-481-8578	Authorized officer COMMISSIONER  Telephone No. 82-42-481-8751
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Form PCT/ISA/226 (July 2014)

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for six months(expire date : **2017.10.20**) from the date of mailing of the international search report.

<http://www.kipo.go.kr/en/> => PCT Services => PCT Services

ID : PCT international application number

PW : **2W532358**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: <http://www.ipkcenter.com>

Email: ipkc@ipkcenter.com

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1036609	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2017/013974	International filing date (<i>day/month/year</i>) 18 January 2017 (18.01.2017)	(Earliest) Priority Date (<i>day/month/year</i>) 19 January 2016 (19.01.2016)
Applicant CORCEPT THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- the international application in the language in which it was filed
 a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

- b. This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).
c. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. **Certain claims were found unsearchable** (See Box No. II)

3. **Unity of invention is lacking** (See Box No. III)

4. With regard to the title,

- the text is approved as submitted by the applicant.
 the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
 the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1
 as suggested by the applicant.
 as selected by this Authority, because the applicant failed to suggest a figure.
 as selected by this Authority, because this figure better characterizes the invention.
b. none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/013974

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-8, 25-41
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-8 and 25-41 pertain to diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and Rule 39.1(iv).
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/00(2006.01)i, G01N 33/74(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
A61B 5/00; G01N 33/50; A61N 2/00; A61F 7/00; G01N 33/74Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility modelsElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & keywords: Cushing's disease, ectopic Cushing's syndrome, ACTH-dependent Cushing's syndrome, baseline, cortisol, ACTH, GRA**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014-0170768 A1 (EHRENKRANZ, J. R. L.) 19 June 2014 See abstract: claims 1-10.	9-24
A	RITZEL, K. et al., 'ACTH after 15 min distinguishes between Cushing's disease and ectopic Cushing's syndrome: a proposal for a short and simple CRH test', European Journal of Endocrinology, Vol.173, No.2, pp.197-204 (2015) See abstract: pages 198 and 199.	9-24
A	REYMONDO, G. et al., 'The corticotrophin-releasing hormone test is the most reliable noninvasive method to differentiate pituitary from ectopic ACTH secretion in Cushing's syndrome', Clinical Endocrinology, Vol.58, pp.716-724 (2003) See summary: pages 719-721.	9-24
A	EL-SHAFIE, O. T. et al., 'Adrenocorticotrophic hormone-dependent Cushing's syndrome: use of an octreotide trial to distinguish between pituitary or ectopic sources', Sultan Qaboos University Medical Journal, Vol.15, Issue 1, pp.e120-123 (Epub. 21 January 2015) See abstract: page e122.	9-24
A	US 2004-0138516 A1 (OSORIO, I. et al.) 15 July 2004 See abstract: claims 25-30.	9-24

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents.	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
20 April 2017 (20.04.2017)Date of mailing of the international search report
20 April 2017 (20.04.2017)

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon, 35298, Republic of Korea

Facsimile No. +82-42-481-8578

Authorized officer
KIM, Yeon Kyung

Telephone No. +82-42-481-3325



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/013974

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014-0170768 A1	19/06/2014	None	
US 2004-0138516 A1	15/07/2004	AU 2003-287162 A1	04/05/2004
		EP 1558334 A2	03/08/2005
		EP 1558334 A4	12/11/2008
		EP 1558334 B1	18/03/2015
		US 8543214 B2	24/09/2013
		WO 2004-036377 A2	29/04/2004
		WO 2004-036377 A3	29/07/2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MAO, YIFAN

KILPATRICK TOWNSEND & STOCKTON LLP
MAILSTOP: IP DOCKETING - 22 1100 PEACHTREE
STREET, SUITE 2800 ATLANTA GA 30309 USA

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **20 April 2017 (20.04.2017)**

Applicant's or agent's file reference
1036009

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2017/013974

International filing date (day/month/year)

18 January 2017 (18.01.2017)

Priority date(day/month/year)

19 January 2016 (19.01.2016)

International Patent Classification (IPC) or both national classification and IPC

A61B 5/00(2006.01)i, G01N 33/74(2006.01)i

Applicant

CORCEPT THERAPEUTICS, INC.

1 This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability, citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon,
35208, Republic of Korea
Facsimile No. +82-42-481-8578



Date of completion of this opinion

20 April 2017 (20.04.2017)

Authorized officer

KIM, Yeon Kyung

Telephone No. +82-42-481-3325



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2017/013974

Box No. 1 Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - the international application in the language in which it was filed
 - a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
2. This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. forming part of the international application as filed:
 - in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
 - b. furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. furnished subsequent to the international filing date for the purposes of international search only:
 - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

international application No.
PCT/US2017/013974

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application

claims Nos. 1-8, 25-41

because:

the said international application, or the said claims Nos. 1-8, 25-41

relate to the following subject matter which does not require an international search (*specify*):

The subject matter of claims 1-8 and 25-41 relates to diagnostic methods practiced on human body (PCT Rules 43 bis.1(b), Rule 67.1(iv)).

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

no international search report has been established for said claims Nos. 1-8, 25-41

a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2017/013974

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	9-24	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	9-24	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	9-24	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

- D1: US 2014-0170768 A1 (EHRENKRANZ, J. R. L.) 19 June 2014
 D2: European Journal of Endocrinology, Vol.173, No.2, pp.197-204 (2015)
 D3: Clinical Endocrinology, Vol.58, pp.718-724 (2003)
 D4: Sultan Qaboos University Medical Journal, Vol.15, Issue 1, pp.e120-123 (Epub. 21 January 2015)
 D5: US 2004-0138516 A1 (OSORIO, I. et al.) 15 July 2004

1. Novelty and Inventive Step

1.1 Claims 9-24

D1, which is considered to be the closest prior art to the subject matter of claims 9 and 15, discloses a method for assessing pituitary function, comprising: providing a subject; administering to the subject a dosage of a glucocorticoid antagonist; and monitoring adrenocorticotrophic hormone ("ACTH") and/or cortisol levels in the subject, wherein subjects having normal pituitary function show an increase in ACTH and/or cortisol levels following glucocorticoid antagonist therapy, and wherein subjects having abnormal pituitary function show substantially no significant change in ACTH and/or cortisol following glucocorticoid antagonist therapy (see claim 1).

The subject matter of claims 9 and 15 mainly differs from that of D1 in the following features: 1) Claims 9 and 15 relate to distinguishing Cushing's disease from ectopic Cushing's syndrome, while D1 relates to distinguishing Cushing's disease from Cushing's syndrome. 2) Claim 15 employs the computing system for the distinguishing Cushing's disease from ectopic Cushing's syndrome. 3) Claims 9 and 15 present the specific distinguishing indication for the distinguishing Cushing's disease from ectopic Cushing's syndrome, wherein the indication uses

Continued on Supplemental Box

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2017/013974

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

- The phrases "baseline adrenocorticotrophic hormone (ACTH)", "the second set values" and "a ratio of the cortisol to the ACTH level" of claim 9 are considered to be writing errors for "baseline adrenocorticotrophic hormone (ACTH) level", "the second set of values" and "a ratio of the cortisol level to the ACTH level", respectively (PCT Article 6).

- Claims 10-12 are worded in reference to "the output module" and "the comparison engine", etc. of claim 15. However, said terms have not been worded in claim 15. Therefore, claims 10-12 are not clear and concise contrary to PCT Article 6. Claims 10-12 have been technically considered to refer to "The system of claim 9", instead of "The method of claim 15".

- The phrase "the pre-determined treatment protocol" of claim 16 is considered to be a writing error for "the predetermined protocol" (PCT Article 6).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box No. V

the differential relationship between the pre-GRA treatment values and the post-GRA treatment values.

These different features are not disclosed or suggested in any of the other prior art documents D2-D5. Accordingly, claims 9 and 15 are neither anticipated nor obvious to a person skilled in the art by the prior documents, taken alone or in combination. Therefore, claims 9 and 15 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

Dependent claims 10-14 and 16-24 are also novel and involve an inventive step under PCT Article 33(2) and (3).

2. Industrial Applicability

Claims 9-24 are industrially applicable under PCT Article 33(4).

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 April 2009 (23.04.2009)

PCT

(10) International Publication Number
WO 2009/050136 A3

(51) International Patent Classification:

A61K 31/00 (2006.01) A61K 45/06 (2006.01)
A61K 31/03 (2006.01) A61P 43/00 (2006.01)
A61K 31/56 (2006.01) A61K 31/444 (2006.01)

(21) International Application Number:

PCT/EP2008/063699

(22) International Filing Date: 13 October 2008 (13.10.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/960,856 17 October 2007 (17.10.2007) US

(71) Applicant (for all designated States except US): **LABORATOIRE HRA PHARMA** [FR/FR]; 15 rue Béranger, F-75003 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ULMANN, André** [FR/FR]; 23 rue Pascal, F-75005 Paris (FR). **GAINER, Erin** [US/FR]; 3 rue des Blancs Manteaux, F-75004 Paris (FR). **VUILLET, François** [FR/FR]; 60-64 rue d'Auteuil, F-75016 Paris (FR).

(74) Agents: **CHAJMOWICZ, Marion** et al.; Becker & Associés, 25 rue Louis Le Grand, F-75 002 Paris (FR).

(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, BR, BW, BY, BZ, CA, CH, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

2 July 2009

(54) Title: GLUCOCORTICOID RECEPTOR ANTAGONISTS SUCH AS MIFEPRISTONE FOR TREATING CUSHING' S SYNDROME

(57) Abstract: The invention relates to a method for treating Cushing s syndrome in a patient, which method comprises administering the patient with a pharmaceutical composition comprising a glucocorticoid receptor antagonist, at least twice a day, or an extended- release composition of a glucocorticoid receptor antagonist, or a combination of a glucocorticoid receptor antagonist and a inhibitor of cortisol synthesis.

WO 2009/050136 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/063699

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/00 A61K31/03 A61K31/56 A61K45/06 A61P43/00
 A61K31/444

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/014394 A (CORCEPT THERAPEUTICS INC [US]; CLARK ROBIN D [US]; RAY NICHOLAS C [GB]) 9 February 2006 (2006-02-09) cited in the application See compounds 31, 33, 35 paragraph [0064]	1-5, 9-14
X	WO 2005/070893 A (CORCEPT THERAPEUTICS INC [US]; CLARK ROBIN D [US]; RAY NICHOLAS C [GB]) 4 August 2005 (2005-08-04) paragraph [0190]; claims ----- -/--	1-5, 9, 11-14

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

3 February 2009

Date of mailing of the international search report

06/05/2009

Name and mailing address of the ISA/
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer
 Herrera, Suzanne

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/063699

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LELY VAN DER A-J ET AL: "RAPID REVERSAL OF ACUTE PSYCHOSIS IN THE CUSHING SYNDROME WITH THE CORTISOL-RECEPTOR ANTAGONIST MIFEPRISTONE (RU 486)" ANNALS OF INTERNAL MEDICINE, NEW YORK, NY; US, US, vol. 114, no. 2, 15 January 1991 (1991-01-15), page 143/144, XP002041041 ISSN: 0003-4819 the whole document	1-8, 11-14
X	CHU J W ET AL: "Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486)" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, ENDOCRINE SOCIETY, CHEVY CHASE, MD, vol. 86, no. 8, 1 August 2001 (2001-08-01), pages 3568-3573, XP002410091 ISSN: 0021-972X abstract page 3570, left-hand column, paragraph 2 - page 3571, left-hand column, paragraph 1	1-8, 11-14
X	WO 2005/087769 A (CORCEPT THERAPEUTICS INC [US]; CLARK ROBIN D [US]; RAY NICHOLAS C [GB]) 22 September 2005 (2005-09-22) cited in the application claims 30,31 paragraph [0229]	1-5,9-14
P,X	WO 2008/060391 A (MERCK & CO INC [US]; BUNGARD CHRISTOPHER J [US]; MANIKOWSKI JESSE J [U]) 22 May 2008 (2008-05-22) claims 3-5 page 15, lines 10-17	1-5,9, 11-14
P,X	BENAGIANO GIUSEPPE ET AL: "Selective progesterone receptor modulators 3: use in oncology, endocrinology and psychiatry." EXPERT OPINION ON PHARMACOTHERAPY OCT. 2008, vol. 9, no. 14, October 2008 (2008-10), pages 2487-2496, XP009110411 ISSN: 1744-7666 abstract page 2491, left-hand column, paragraph 2-6	1-8, 11-14
A	WO 2004/041215 A (CORCEPT THERAPEUTICS INC [US]; BELANOFF JOSEPH K [US]) 21 May 2004 (2004-05-21) paragraph [0026]	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/063699

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically: .

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14

The use of a glucocorticoid receptor antagonist such mifepristone for the treatment of Cushing's syndrome, wherein the active ingredient is adapted for administration at least twice a day

2. claims: 15-27

The use of a glucocorticoid receptor antagonist such mifepristone for the treatment of Cushing's syndrome, wherein the active ingredient is present in an extended release composition

3. claims: 28-38

The use of a glucocorticoid receptor antagonist such mifepristone together with an inhibitor or cortisol synthesis such as mitotane for the treatment of Cushing's syndrome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/063699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006014394 A	09-02-2006	AU 2005270039 A1	09-02-2006
		CA 2572544 A1	09-02-2006
		EP 1778236 A1	02-05-2007
		JP 2008505117 T	21-02-2008
		KR 20070039579 A	12-04-2007
		US 2006025405 A1	02-02-2006
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		CA 2552419 A1	04-08-2005
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CA 2558899 A1	22-09-2005		
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ES 2313317 T3	01-03-2009		
HK 1104813 A1	03-04-2009		
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		EP 1581234 A2	05-10-2005
		EP 1567167 A2	31-08-2005
		JP 2006508951 T	16-03-2006
		JP 2006507311 T	02-03-2006
		WO 2004041214 A2	21-05-2004

Electronic Acknowledgement Receipt

EFS ID:	30555673
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Yifan Mao/Jo Ann Honcik Dallara
Filer Authorized By:	Yifan Mao
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	03-OCT-2017
Filing Date:	19-JUN-2017
Time Stamp:	16:48:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS2.pdf	227158 <small>fc0567dbfaa3e07cf28038a8dc600bc58eab12ad</small>	yes	7

Multipart Description/PDF files in .zip description					
Document Description			Start	End	
Transmittal Letter			1	2	
Information Disclosure Statement (IDS) Form (SB08)			3	7	
Warnings:					
Information:					
2	Foreign Reference	B1_FR_WO08060391.PDF	3716940	no	117
			0a18aed62cf56e825c2d96219bd01f9aeed2c242		
Warnings:					
Information:					
3	Foreign Reference	B2_FR_WO2009050136_A2.pdf	1552305	no	22
			32a26a399d78ea7bc76926d2446290f28235278b		
Warnings:					
Information:					
4	Non Patent Literature	B3_NPL_Albertson.PDF	1286767	no	6
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Information:					
5	Non Patent Literature	B4_NPL_Asser.PDF	402911	no	9
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6	Non Patent Literature	B5_NPL_Benagiano_2008.PDF	279572	no	10
			0151baac40149f2405f9d14e5190365e607deb5b		
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7	Non Patent Literature	B6_NPL_Bertagna.PDF	585914	no	5
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8	Non Patent Literature	B7_NPL_Chrousos.PDF	2697668	no	6
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Information:					
9	Non Patent Literature	B8_NPL_Chu.PDF	151192	no	6
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Information:					
10	Non Patent Literature	B9_NPL_Cuneo_1997.PDF	9531344	no	12
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Warnings:					
Information:					
11	Non Patent Literature	B10_NPL_Ehrenkranz.PDF	70511	no	2
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12	Non Patent Literature	B11_NPL_El-Shafie.PDF	486527	no	4
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Information:					
14	Non Patent Literature	B13_NPL_Gross.PDF	849331	no	6
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Warnings:					
Information:					

15	Non Patent Literature	B14_NPL_Healy.PDF	360465	no	3
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Warnings:					
Information:					
16	Non Patent Literature	B15_NPL_Lee.PDF	10330202	no	120
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18	Non Patent Literature	B17_NPL_MEDLINE_PLUS_2005.PDF	218279	no	4
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Information:					
19	Non Patent Literature	B18_NPL_Moncet_2007.PDF	178589	no	6
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Information:					
20	Non Patent Literature	B19_NPL_Reimondo.PDF	103637	no	7
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Information:					
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Information:					

22	Non Patent Literature	B21_NPL_SARKAR_2002.PDF	863367	no	8
			496e8e32bb1dea5f9373a7965b200ce2555eab8a		
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Information:					
23	Non Patent Literature	B22_NPL_Tsigos.PDF	105895	no	21
			026d6a567c441f55e8039a43927ab757daacc0bf		
Warnings:					
Information:					
24	Other Reference-Patent/App/Search documents	B23_NPL_PCTUS2017013974_I SRandWO.PDF	772057	no	12
			9e261d6f30c41d843e17c0e6c58192384388661c		
Warnings:					
Information:					
25	Other Reference-Patent/App/Search documents	B24_NPL_PCTEP2008063699_I SR_Uhlmann_WO2009050136.PDF	237446	no	6
			f0675b0295a326eb441633493cc0c2bac ec244		
Warnings:					
Information:					
26	Non Patent Literature	B25_NPL_Korlym_Label_Oct_2016.pdf	388661	no	21
			a928f726c2e2af7f448be8aedec76461b6016464		
Warnings:					
Information:					
27	Other Reference-Patent/App/Search documents	B26_15627368_NFOA_2017-08-08.PDF	501993	no	13
			095e6d8a20bcc6ab25621b983cb560c9fee36712		
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Total Files Size (in bytes):			37095122		

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 a 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.

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on October 3, 2017

PATENT
Attorney Docket No.: 085178-1053027-011410US

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT

ADMINISTRATION OF
GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A
INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner:

Technology Center/Art Unit: 1629

INFORMATION DISCLOSURE
STATEMENT

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

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner.

The following application is related to this application: 15/627,368, filed June 19, 2017. Copies of any Office Actions in such Patent Applications are available via the USPTO's PAIR or electronic file wrapper system and are believed to be readily accessible to the Examiner. Thus, although Applicant may submit copies of some such Office Actions, Applicant does not represent that copies of all, or the most significant, Office Actions are being supplied. If the

Examiner desires copies of all such Office Actions, the Examiner should contact the undersigned.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

This Information Disclosure Statement is being filed before the mailing date of the first Office Action on the merits.

Applicant believes that no fee is required for submission of this statement. However, if any additional fees are due for the submission of this Information Disclosure Statement, please deduct those fees from Deposit Account No. 20-1430.

Respectfully submitted,

/Yifan Mao/

Yifan Mao
Registration No. 60,804

KILPATRICK TOWNSEND & STOCKTON LLP

Attachment



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
15/627,359 06/19/2017 Joseph K. Belanoff 085178-1053027-011410US 2957

144579 7590 10/20/2017
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
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1100 Peachtree Street
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Atlanta, GA 30309

EXAMINER

SIMMONS, CHRIS E

ART UNIT PAPER NUMBER

1629

NOTIFICATION DATE DELIVERY MODE

10/20/2017

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):

- ipefiling@kilpatricktownsend.com
jfox@corcept.com
KTSDocketing2@kilpatrick.foundationip.com

Art Unit: 1629

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Priority

This application claims the benefit of and priority to U.S. Provisional Application Serial No. 62/465,772, filed March 1, 2017, and U.S. Provisional Application Serial No. 62/466,867, filed March 3, 2017.

Information Disclosure Statement

The Information Disclosure Statement(s) filed 6/19/2017 has/have been considered by the Examiner. The submission(s) is/are in compliance with the provisions of 37 CFR §§ 1.97 and 1.98. Enclosed with this Office Action is a return-copy of the Forms PTO-1449 with the Examiner's signature and indication of those references that have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

Art Unit: 1629

matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 1, 10 and 19 recites the limitation "the daily dose". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1-30 is/are rejected under 35 U.S.C. 103 as being unpatentable over Korlym™ (mifepristone) [package insert]. Corcept Therapeutics, Inc., Menlo Park, CA; Feb. 2012. 26 pages in view of Ulmann (US 2010/0261693).

Art Unit: 1629

Claimed invention

Claim 1. A method of **treating Cushing's syndrome** in a patient who is taking a **glucocorticoid receptor antagonist (GRA)** comprising reducing the daily dose of said GRA from an original dose to an adjusted dose that is **at least 33% less than said original dose** when the patient is receiving concomitant administration of a **CYP3A inhibitor**.

Claim 10. A method of **treating symptoms associated with elevated cortisol levels** in a patient who is taking a **glucocorticoid receptor antagonist (GRA)** comprising reducing the daily dose of said GRA from an original dose to an adjusted dose that is **at least 33% less than said original dose** when the patient is receiving concomitant administration of a **CYP3A inhibitor**.

Claim 19. A method of **controlling hyperglycemia secondary to hypercortisolism** in a patient with endogenous Cushing's syndrome who is taking a **glucocorticoid receptor antagonist (GRA)** comprising reducing the daily dose of said GRA from an original dose to an adjusted dose that is **at least 33% less than said original dose** when the patient is receiving concomitant administration of a **CYP3A inhibitor**.

Claim 28. A method of **controlling hyperglycemia secondary to hypercortisolism** in a patient with endogenous Cushing's syndrome comprising administering a daily dose of **600 milligrams (mg) mifepristone** when the patient is receiving **concomitant administration of a CYP3A inhibitor**.

Prior art

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The Korlym™ package insert teaches that Korlym™ (**mifepristone**) is a cortisol receptor blocker indicated to **control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome** who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. See package insert, “Indications and Usage” at page 1. The amount of mifepristone is adjusted based on clinical response and tolerability. See package insert, “Dosage and Administration” at page 1. The dose may be increased in 300 mg increments to a maximum of 1200 mg. See Id. In a study for treating Cushing’s syndrome, the dose of mifepristone was increased from 300 mg to 600 mg, then to 900 mg for patients under 60kg or 1200 mg for patients over 60 kg based on clinical tolerance and clinical response. See paragraph bridging pages 15 and 16. Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required. See package insert, 7.2 CYP3A Inhibitors at page 9. **Mifepristone** should be used with extreme caution in patients taking **ketoconazole** and other strong inhibitors (e.g., itraconazole, nefazodone, ritonavir, etc.) of CYP3A. See package insert, “5.6 Use of Strong CYP3A Inhibitors” at page 6. Mifepristone should be used in combination with **strong CYP3A inhibitors** only when necessary, and in such cases the dose should be limited to **300 mg per day**. See Id.

While the Korlym™ (mifepristone) package insert teaches the use of mifepristone for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome and further teaches the treatment of patients with Cushing’s syndrome with 300 mg, 600 mg and 1200 mg mifepristone, it *does not expressly teach the patient receiving an original dosage that is subsequently decreased by at least 33%*. However, the package insert

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further teaches mifepristone should be used in combination with strong CYP3A inhibitors, such as ketoconazole, only when necessary, and in such cases the dose should be limited to 300 mg per day. Ulmann teaches that mifepristone and an inhibitor of cortisol synthesis such as ketoconazole, mitotane, metyrapone, aminoglutethimide, or fluconazole may be used to treat Cushing syndrome. See [0006], [0052], [0053].

The claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because both references teach the use of mifepristone for treating Cushing's syndrome. Both reference also teach that ketoconazole can be combined with mifepristone, where Ulmann more specifically teaches that the combination of mifepristone and ketoconazole is useful for treating Cushing's syndrome.

One of ordinary skill in the art would have found it obvious to treat hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome with a composition containing mifepristone and ketoconazole. The artisan would have understood that both mifepristone and ketoconazole are taught to be used for treating Cushing's diseases and may be combined as may be combined for that purpose (Ulmann). When combined, the artisan would have further recognized that the dose of mifepristone should be low, at 300 mg. Thus, if the Cushing's patient is treated with 1200 mg, 900 mg, or 600 mg as disclosed by the package insert and it is found to be beneficial to combine with ketoconazole, then the artisan would have understood that the concentration of mifepristone should be adjusted as tolerated to 300 mg, for example (see package insert). Accordingly, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

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Claim 2 depends from Claim 1, wherein said original dose is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted dose is 600 mg per day of said GRA. Claim 3 depends from Claim 1, wherein said original dose is 600 milligrams (mg) per day of said GRA, and said adjusted dose is 300 mg per day of said GRA, further comprising titrating the adjusted dose to a maximum of 600 mg per day of said GRA. The package insert provides clear guidance that the concentration of mifepristone should be adjusted as tolerated by the patient and further state that when mifepristone is combined with a strong CYP3A inhibitor such as ketoconazole, the amount of mifepristone should be adjusted and more particularly adjusted to 300 mg. While the prior art does not specifically lower mifepristone dosage to 600 mg, one of ordinary skill in the art would have understood that while lowering it to 300mg is the more preferred dose of mifepristone when combine with ketoconazole, the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment. Claims 11 and 12 are similar to Claims 2 and 3 but depend from Claim 10 and are prima facie obvious for similar reasons. The same is true for Claims 20 and 21, which depend from Claim 19.

Claims 4-6 depend from Claims 1-3, respectively, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor. Both Ulmann and the package insert teach the combination use of mifepristone and ketoconazole, whereas Ulmann specifically teaches their combination for treating Cushing's disease. Claims 13-15 are similar to Claims 4-6 and are prima facie obvious for similar reasons. The same is true for Claims 22-24, which depend from Claims 19-21, respectively.

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Claims 7-9 depend from Claims 1, 4, and 5, respectively, wherein said CYP3A inhibitor is ketoconazole. Claims 16-18 depend from Claims 10, 13 and 14, respectively, wherein said CYP3A inhibitor is ketoconazole. These claims are rendered prima facie obvious as outlined for Claims 4-6 and 13-15 above. The same is true for Claims 25-27 and 29, which depend from Claims 19, 22, 23 and 28, respectively.

Claim 30 depends from Claim 29, wherein said daily dose of mifepristone is titrated up to 600 mg per day from 300 mg per day. As outlined above, the package insert teaches that the adjustment of dose of mifepristone based on clinical tolerance and clinical response. Thus, one of ordinary skill in the art would have understood that while lowering it to 300mg is the more preferred dose of mifepristone when combine with ketoconazole, the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM Eastern.

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

Art Unit: 1629

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, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CHRIS SIMMONS/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

Notice of References Cited	Application/Control No. 15/627,359	Applicant(s)/Patent Under Reexamination BELANOFF, JOSEPH K.	
	Examiner CHRIS SIMMONS	Art Unit 1629	Page 1 of 1

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C	US-				
D	US-				
E	US-				
F	US-				
G	US-				
H	US-				
I	US-				
J	US-				
K	US-				
L	US-				
M	US-				

FOREIGN PATENT DOCUMENTS

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
N					
O					
P					
Q					
R					
S					
T					

NON-PATENT DOCUMENTS

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
*	Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)				
U	Korlym™ (mifepristone) [package insert]. Corcept Therapeutics, Inc., Menlo Park, CA; Feb. 2012. 26 pages.				
V					
W					
X					

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		
	Filing Date		herewith
	First Named Inventor	Joseph K. Belanoff	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		085178-1053027-011410US

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
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Examiner Initials*	Cite No	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 ⁵
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	First Named Inventor	Joseph K. Belanoff	
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	Examiner Name		
	Attorney Docket Number		085178-1053027-011410US

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EXAMINER SIGNATURE			
Examiner Signature	/CHRIS E SIMMONS/	Date Considered	10/10/2017
<p>*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			
<p>¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.</p>			

Search Notes 	Application/Control No. 15627359	Applicant(s)/Patent Under Reexamination BELANOFF, JOSEPH K.
	Examiner CHRIS SIMMONS	Art Unit 1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

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
EAST, Inventor search	9/17/2017	CS
Google : "mifepristone adjusting dosage"; "mifepristone CYP450 3A inhibitors is necessary, the dose should be limited to 300 mg per day"	9/17/2017	CS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	6	((("CORCEPT") near3 ("THERAPEUTICS") near3 ("INC")).AANM.	USPAT	AND	OFF	2017/09/17 21:29
S2	17	((("BELANOFF") near3 ("Joseph")).INV.	USPAT	AND	OFF	2017/09/17 21:29
S3	8432	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/17 21:29
S4	23195	ketoconazole	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/17 21:30
S5	23	S2 or S1	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/17 21:30
S6	8	S5 S3 S4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/17 21:30
S7	43	((("BELANOFF") near3 ("Joseph")).INV.	US-PGPUB; USPAT; USOCR	AND	OFF	2017/09/17 21:34
S8	291	((("CORCEPT") near3 ("THERAPEUTICS") near3 ("INC")).AANM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/17 21:34
S9	331	S7 or S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/17 21:34
S10	23195	ketoconazole	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/18 09:00
S11	1444	S10 cushing	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/18 09:00
S12	12	S10 cushing.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2017/09/18 09:00

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15/627,359	
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	First Named Inventor	Joseph K. Belanoff		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	085178-1053027		

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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

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	Attorney Docket Number	085178-1053027	

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	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	085178-1053027	

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	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	085178-1053027	

	B25.	FDA Label for KORLYM [®] dated October 2016	
	B26.	15/627,368, "Non-Final Office Action", August 8, 2017, 13 pages	

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	First Named Inventor	Joseph K. Belanoff		
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	Examiner Name	Chris E Simmons		
	Attorney Docket Number	085178-1053027-011410US		

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Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	C1	20170281651	A1	Oct 5, 2017	BELANOFF	

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Electronic Patent Application Fee Transmittal

Application Number:	15627359			
Filing Date:	19-Jun-2017			
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS			
First Named Inventor/Applicant Name:	Joseph K. Belanoff			
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara			
Attorney Docket Number:	085178-1053027-011410US			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
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Total in USD (\$)				90

Electronic Acknowledgement Receipt

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Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
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1		IDS3.pdf	158537	yes	3
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	Document Description	Start	End	
	Transmittal Letter	1	2	
	Information Disclosure Statement (IDS) Form (SB08)	3	3	

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30968	no	2
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a 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.

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on November 1, 2017

PATENT
Attorney Docket No.: 085178-1053027-011410US

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT

ADMINISTRATION OF
GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A
INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: Chris E Simmons

Technology Center/Art Unit: 1629

INFORMATION DISCLOSURE
STATEMENT

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

Commissioner:

The reference cited on attached form PTO/SB/08A is being called to the attention of the Examiner. In accordance with the provisions of 37 CFR §1.98(a)(2), copies of any cited U.S. Patent and U.S. Patent Application Publications are not provided.

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

This Information Disclosure Statement is being filed after the mailing of the first Office Action on the merits, but before the mailing date of the final Office Action, Notice of Allowance, or any other action that closes prosecution.

The Commissioner is authorized to charge the fee set forth in §1.17(p) to the firm's credit card for consideration of this paper. The Commissioner is authorized to charge any additional fee due to Deposit Account No. 20-1430.

Respectfully submitted,

/Kenneth A. Weber/

Kenneth A. Weber
Registration No. 31,677

KILPATRICK TOWNSEND & STOCKTON LLP

Attachment



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Table with 4 columns: APPLICATION NUMBER (15/627,359), FILING OR 371(C) DATE (06/19/2017), FIRST NAMED APPLICANT (Joseph K. Belanoff), ATTY. DOCKET NO./TITLE (085178-1053027-011410US)

CONFIRMATION NO. 2957

PUBLICATION NOTICE

144579
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
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1100 Peachtree Street
Suite 2800
Atlanta, GA 30309



Title: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

Publication No. US-2017-0326157-A1

Publication Date: 11/16/2017

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joe Belanoff et al.

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION
OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: Chris E. SIMMONS

Technology Center/Art Unit: 1629

DECLARATION OF JOSEPH K.
BELANOFF UNDER 37 C.F.R. § 1.132

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

Commissioner:

I, Dr. Joseph K. Belanoff, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. My *curriculum vitae* is filed as an Appendix to this Declaration.
2. I am the Chief Executive Officer (CEO) of Corcept Therapeutics, Inc., whose primary mission is to provide improved medicine for a variety of illnesses based on targeting glucocorticoid signaling. I have been at this position and related positions since 1999. I am a Board Certified psychiatrist. I received an M.D. in 1992 from Columbia University, College of Physicians and Surgeons. I took my residency and fellowship training in psychiatry at the Stanford School of Medicine.
3. I am the inventor of the subject application.

4. I have read and am familiar with the contents of the application, as well as the Office Action mailed October 20, 2017, and the references cited therein.

5. I understand that the Patent Office has rejected the pending claims as obvious under 35 U.S.C. § 103(a) over the Korlym[®] package insert and U.S. patent publication 2010/0261693 by Uhlmann et al.

6. I note that the present invention arose out of our investigations into the safety of co-administering mifepristone along with CYP3A inhibitors such as ketoconazole. The belief in the art, as forcefully indicated by the warning the FDA required in the Korlym[®] package insert, was that such co-administration would be dangerous. The FDA warning stated that mifepristone should be limited to 300 mg per day if administered with a strong CYP3A inhibitor. It was expected that the CYP3A inhibitor would reduce mifepristone metabolism to such a degree that mifepristone concentrations would be dangerously high if administered with a CYP3A inhibitor. Clinicians typically assume that FDA dose limitations are founded in clinical experience, and would expect adverse reactions if exceeded.

7. However, despite these warnings, it was possible that some physician might, out of ignorance or out of failure of other treatments in a difficult case, try to treat a patient with both mifepristone and a CYP3A inhibitor. We thus felt it important to determine whether or not there might be a safe way to treat patients with both types of drugs, if a physician decided to risk such co-administration of mifepristone with a CYP3A inhibitor.

8. As disclosed in the present application, we found that, surprisingly, the increase in mifepristone concentration when administered with ketoconazole was much smaller than expected. The expectation was that ketoconazole would increase mifepristone levels by 4 to 5 times. Instead, the increase in mifepristone levels caused by ketoconazole was 0.3 times. We also surprisingly found that such co-administration was manageable, and allowed for safe methods of treatment with both drugs. By reducing the mifepristone dose by 33% when administering a CYP3A inhibitor such as ketoconazole, the mifepristone concentration remained within safe, and effective, levels. It was further surprisingly found that in some cases, the mifepristone dose could be titrated upwardly, after the initial reduction, to provide effective treatment while mifepristone levels remained within safe bounds.

9. As disclosed in the present application, we further found that, surprisingly, the amount of mifepristone that could safely be administered along with a CYP3A inhibitor such as ketoconazole was greater than 300 mg; our data indicated that 600 mg, 900 mg, and 1200 mg of mifepristone could be safely administered with ketoconazole. For example, the present methods allow for safe and effective mifepristone administration by reducing the mifepristone dose (such as these doses of 600 mg, 900 mg, and 1200 mg) by at least 33% when administering a CYP3A inhibitor such as ketoconazole. This was surprising in view of the limited mifepristone level recited in our FDA-approved package insert.

10. We were surprised by these results. Based on my clinical knowledge and experience, I believe that those of skill in the art would also have found these results surprising, in view of the expectation that the CYP3A inhibitor would greatly increase mifepristone levels, in view of the warning required by the FDA, and also in view of the known variability in patient response to administered mifepristone, which would have been expected to increase the variability of effects possibly into dangerous levels. Instead, the present application discloses our surprising discovery that, by reducing the mifepristone dose when also administering a CYP3A inhibitor, both mifepristone and a CYP3A inhibitor can be safely administered together. The present methods, which provide safe methods for concomitant administration of mifepristone with a CYP3A inhibitor, provide a further useful tool for treating Cushing's syndrome.

11. The Office also cites Uhlmann in addition to the Korlym[®] package insert, suggesting that, since "both references teach the use of mifepristone for treating Cushing's syndrome ... that ketoconazole can be combined with mifepristone", and "where Ulmann more specifically teaches that the combination of mifepristone and ketoconazole is useful for treating Cushing's syndrome" (page 6). However, our methods require more than merely the combination of mifepristone and ketoconazole.

12. As noted above, those of skill in the art, including the FDA, expected that the combination of mifepristone and ketoconazole might result in excessive mifepristone levels, which might be dangerous or therapeutically counterproductive. Ulmann provides no method to avoid this possible deleterious outcome; instead, Ulmann suggests multiple doses per day, in order to avoid excess cortisol levels. Even if one were to follow Uhlmann, one would not be led to the present methods which require once per day administration of mifepristone, where the amount of mifepristone is reduced by at

least 33% from the dose administered in the absence of a CYP3A inhibitor. Thus, Ulmann provides no suggestion to those of skill in the art that solves the possible problems of combining mifepristone with ketoconazole, and does not suggest the present methods.

13. Accordingly, based on my clinical experience, my experience in the field of Cushing's syndrome treatments, and based on my review of the application and literature, it is my opinion that those of skill in the art would have found the methods now claimed, and the results of the practice of those methods, to be surprising and unexpected.

14. This Declarant has nothing further to say.

Dated:

December 15, 2017



Joseph K. Belanoff, M.D.

Attachment: Belanoff *curriculum vitae* as an Appendix

CURRICULUM VITAE

Name: Joseph K. Belanoff, M.D.
Mailing Address: One Southgate Drive, Woodside, CA 94062
Date of Birth: August 12, 1957
Place of Birth: New York, New York
CA Medical License #: G77733

1999-present: CEO, Corcept Therapeutics Incorporated, Menlo Park, California

Education:

1975-1979 B.A. Amherst College, Amherst, Massachusetts
1986- 1988 Pre-Med Studies New York University & Hunter College, New York, New York
1988-1992 M.D. Columbia University, New York, New York

Postdoctoral Training:

1992-1996 Resident in Psychiatry, Stanford University School of Medicine, California

Licensure and Certification:

1993 National Board of Medical Examiners
1998, 2008 American Board of Psychiatry and Neurology

Academic Appointments:

1992 Student Representative, Robert Wood Johnson Foundation site visit for evaluation, design, and implementation of a new medical school curriculum
1995-1998 Instructor for Psychopharmacology, Pacific Graduate School of Psychology Palo Alto, California
1997-1999 Instructor in Psychiatry, Stanford University School of Medicine
1997-2001 Director, Residency Education, Palo Alto Veteran's Administration Health Care System, Menlo Park Division
1999-2001 Acting Assistant Professor, Stanford University School of Medicine
2001-present Clinical Instructor, Stanford University School of Medicine

Hospital Appointments:

1995-1997 Research Fellow, Psychiatry & Behavioral Sciences, Stanford University
1997-2001 Director of Clinical Psychopharmacology, Palo Alto Veteran's Administration Health Care System, Menlo Park Division
1997-2001 Staff Psychiatrist, Palo Alto Veteran's Administration Health Care System, Menlo Park Division
1997-present Attending Physician, Psychiatry, Stanford University Medical Center

Other Professional Positions:

1979-1982	Trader for Mabon, Nugent & Co., New York, New York
1980-1985	Instructor for Securities Training Institute, New York, New York
1982-1986	General Partner at Miller Tabak Hirsch & Company, New York, New York
1986-1987	Head Trader for Taxable Fixed Income Securities at Moseley Securities, New York, NY
1987-1989	Consultant for Mabon, Nugent & Co., New York

Awards and Honors:Academic

1975	National Merit Scholarship, Amherst College.
1979	Graduated magna cum laude in English.
1992	Michael H. Aranow Prize, presented to the student who “best exemplifies the caring and humane qualities of the practicing physician.”
1992	Alpha Omega Alpha, Columbia University College of Physicians and Surgeons.
1996	George D. Gulevich, M.D., Award presented to the graduating resident who “demonstrates the highest in humanistic values and excellence in patient care.” Stanford University, Department of Psychiatry
2000	Teacher of the Year, Stanford University, Department of Psychiatry
2010	Teacher of the Year, Stanford University, Department of Psychiatry

Research

1995-1997	Bio-behavioral Fellowship, National Institute of Mental Health: extensive research on the description, etiology, and treatment of psychotic depression.
1997-1999	Young Investigator Award, National Alliance for Research on Schizophrenia and Depression: research on the treatment of psychotic major depression.
1997-1999	Grant Winner, National Institute of Mental Health: research on the relationship between the neurobiology of stress, cognition, and AIDS.
1997-1999	Grant Winner, Nancy Pritzker Foundation: research on the treatment of schizoaffective disorder.
1999-2001	Young Investigator Award, National Alliance for Research on Schizophrenia and Depression: research on the treatment of schizoaffective disorder.

Major Committee Assignments:National and Regional

1995-1997	Resident Advisory Board, Journal of Clinical Psychiatry
1999-present	California Alzheimer’s Disease Advisory Board

Stanford University Medical Center

1993-present	Resident Selection and Advisory Committee
1997-2007	Resident Evaluation Committee
1999-present	General Clinical Research Center Advisory Committee
2002-present	HIPAA Policy Review Committee

Major Research Interest:

Hypothalamic-Pituitary-Adrenocortical Axis Dysfunction

Other Activities:

Interviewer: Steven Spielberg Visual History Foundation

Script Consultant: Melrose Place, The Cosby Show, ER, Providence, The Closer and Major Crimes

Reviewer: The Journal of Nervous and Mental Disease, Biological Psychiatry, Psychosomatics and The Journal of Psychiatric Research

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Book Chapters

1. **Belanoff J**, DeBattista C, Schatzberg A. Adult psychopharmacology. In: Koocher G, Norcross J, Hill S, eds. The Psychologist's Desk Reference. New York City: Oxford University Press. First Ed. (1998), Second Ed. (2005), Third Ed (2011).
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5. **Belanoff J**, Glick I. New psychotropic drugs for axis I disorders: Recently arrived, in development, and never arrived. In: Schatzberg A, Nemeroff C, eds. Textbook of Psychopharmacology. Washington DC: APA Press. 1998.
6. **Belanoff J**, Coleman C, Schatzberg A. Principles of the pharmacotherapy of depression. In: Charney D, ed. Neurobiological Foundation of Mental Illness. New York City: Oxford Press. 1998.
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1. H. Hunt, J. **Belanoff**, K. Donaldson, D. Combs, M. Strem, V. Zann, P. Leung, S. Sweet, A. Connor Assessment of Safety, Tolerability, Pharmacokinetics, Proof of Concept and Proof of Pharmacological Effect of Orally Administered CORT125134 using an Adaptive Clinical Protocol. For: AAPS, Orlando, October 2015.
2. Block Thaddeus, Petrides Georgios, D'Souza Bernadette, **Belanoff Joseph K**. A Double Blind, Placebo-Contrlled, US Multicenter Trial of Mifepristone for the treatment of Major Depressive Disorder (MDD) with Psychotic Features: Interm Analysis of the RECorS Trial, Baseline Characteristics. For: Society of Biological Psychiatry 69th Annual Meeting, New York, May, 2014.
3. **Belanoff Joseph K**, Block Thaddeus S., Nguyen Dat, Cram David, Petrides Georgios. Characteristics of Psychotic Depression Patients with Hallucinations, Delusions, or Both. For: ISAD Congress, Berlin Germany, April 2014
4. **Belanoff, Joseph K**, Blasey, Christine M, Clark, Robin D and Roe, Robert L. Two Selective Glucocorticoid Receptor (Type II) Antagonists Prevent Antipsychotic-Induced Weight Gain. For: APA, Hawaii, Poster, May 2011
5. Asagami T, **Belanoff JK**, Clark RD, and Tsao PS. (2010) Glucocorticoid Antagonists Improve Insulin Sensitivity in Mice. For: Obesity Society, San Diego, Poster, October 2010

6. **Belanoff JK**, Clark RD, Blasey CM, Roe RL. Glucocorticoid Antagonist Attenuates Olanzapine-Induced Weight Gain in Rats. For: Obesity Society, San Diego, Poster, October 2010
7. **Belanoff J**, Gross C, Roe R, Blasey C, Hafez K. Mifepristone Reduces Weight Gain and Metabolic Abnormalities Associated with Risperidone Use. For: WFSBP, Paris France, Poster, July 2009
8. Roe R, Blasey C, **Belanoff J**. Next-Generation GR-II Antagonist Prevents and Reverses Antipsychotic-Induced Weight Gain. For: WFSBP, Paris France, Poster, July 2009
9. Gross C, Blasey C, Roe RL, **Belanoff J**. Mifepristone Prevents Risperidone Induced Weight Gain in Healthy Men. For: ADA, New Orleans, Poster, June 2009
10. Asagami T, Clark RD, **Belanoff J**, Tsao PS. A New Selective Glucocorticoid Antagonist Suppresses Body Weight Gain as Well as Improves Insulin Sensitivity. For: ADA, New Orleans, Poster, June 2009
11. **Belanoff J**, Gross C, Roe R, Blasey C, Hafez K. Mifepristone Reduces Weight Gain Associated with Risperidone Use. For: 40th Annual ISPNE Conference in San Francisco on July 23-26, 2009
12. **Belanoff J**, Gross C, Roe R, Blasey C, Hafez K. Mifepristone Reduces Weight Gain and Metabolic Abnormalities Associated with Risperidone Use. For: CINP Congress, Edinburgh Scotland, Poster, April 2009
13. Roe R, Blasey C, **Belanoff J**. Next-Generation GR-II Antagonist Prevents and Reverses Antipsychotic Induced-Weight Gain. For: CINP Congress, Edinburgh Scotland, Poster, April 2009
14. **Belanoff J**.) Efficacy of Mifepristone for the Prevention of Olanzapine Induced Weight Gain. For: CINP Congress, Munich Germany, Poster, July 2008
15. Schatzberg A, **Belanoff J**. Glucocorticoid receptor antagonists as a novel treatment option in psychotic depression. For: ISPNE, Dresden, Germany, July 2008
16. Beebe, K.L., Block, T., DeBattista, C., Blasey, C., **Belanoff, J**. (2006) Mifepristone for the reduction and prevention of olanzapine-induced weight gain in rats.
17. DeBattista C, **Belanoff J**, Saha G, Schatzberg A. A Double Blind Placebo Controlled trial of CORLUX (Mifepristone) in the Treatments of Psychotic Major Depression. For: NCDEU 2004 Poster, Arizona
18. DeBattista C, **Belanoff J**, Schatzberg A. C-1073 (mifepristone) in the treatment of psychotic major depression, ACNP, San Juan, Puerto Rico, December 2003.
19. Karssen AM, **Belanoff J**, deKloet ER. Access of glucocorticoid receptor antagonist C-1073 (mifepristone/RU486) and cortisol to the brain; interactions at the blood-brain barrier, ISPNE Congress, New York, September 2003
20. Karssen AM, **Belanoff J**, deKloet ER. Glucocorticoid receptor antagonist C-1073 (mifepristone/RU486) inhibits P-glycoprotein-mediated efflux transport of cortisol, ISPNE Congress, Pisa, Italy, March 2003.
21. Wilkinson CW, Hammett JM, Murray AR, **Belanoff J**, Schatzberg AF, Lupien SJ. Mediation of Human Glucocorticoid Feedback Inhibition By Both Mineralocorticoid and Glucocorticoid Receptors at the Circadian Peak, IBRO World Congress of Neuroscience, Prague, Czech Republic, 2003
22. Karssen AM, **Belanoff J**, deKloet ER. Glucocorticoid receptor antagonist C-1073 (RU486) inhibits P-glycoprotein-mediated efflux transport of cortisol, Endoneuro 2003.
23. Karssen AM, **Belanoff J**, deKloet ER. Uptake into the brain of GR-antagonist C-1073. Implications for treatment of psychotic major depression, ISPNE Congress, Pisa, Italy 2003
24. DeBattista C, **Belanoff J**, Saha G, Schatzberg A. Adjunctive Open-Label C-1073 (mifepristone) in the Treatment of Recurrent Psychotic Major Depression in Patients who had Previously

Responded in a Blinded Adjunctive Trial of C-1073 or Placebo, ISPNE Congress, Pisa, Italy 2003.

25. DeBattista C, **Belanoff J**, Schatzberg A. C-1073 (mifepristone) In the Treatment of Recurrent Psychotic Major Depression. ACNP Annual Meeting 2002, Puerto Rico.
26. **Belanoff JK**, Rothchild AJ, Cassidy F, DeBattista C, Baulieu E-E, Schold C, Schatzberg AF. Rapid Reversal of Psychotic Major Depression Using C-1073 (Mifepristone). The 5th International Congress of Neuroendocrinology Conference, Bristol, UK, 2002.
27. Karssen AM, Meijer OC, van der Sandt ICJ, de Boer AG, **Belanoff JK**, de Lange ECM, de Kloet ER. P-glycoprotein, a modulator or glucocorticoid access to the brain. The 5th International Congress of Neuroendocrinology Conference, Bristol, UK, 2002.
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29. Wilkinson C, Peskind E, Raskind M, Hammett J, Beckham R, **Belanoff J**, Schatzberg, A. Human Glucocorticoid Feedback Inhibition Is Mediated Primarily by Type II Corticosteroid Receptors during Morning Hours. ISPNE Meeting, Quebec City, Canada, 2001.
30. Rothschild A, **Belanoff J**, et al. Rapid Reversal of Psychotic Major Depression Using C-1073 (Mifepristone). 2000.
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Koopman C, Gore-Felton C, **Belanoff J**, Sund B, Azimi N, O'Shea K, Ashton E, DeMaria S, Israelski D, Spiegel D, Schatzberg S. Cortisol and acute stress reactions in adults with HIV / AIDS. ISTSS, San Antonio, Texas, 2000.
32. **Belanoff J**, Kennelly J, Saldivar A. Cognitive changes in psychotic major depression. Pacific Research Forum, Palo Alto, California, 1999.
33. **Belanoff J**, Glick I, Ballon J. New psychotropic drugs for axis I disorders: Recently arrived, in development, and never arrived. American Colleges of Neuropharmacology Annual Meeting, San Juan, Puerto Rico, 1998.
34. **Belanoff J**, Glick I. New psychotropic drugs for schizophrenia: Recently arrived, in development, and never arrived. International Congress on Schizophrenia Research Annual Meeting, Colorado Springs, Colorado, 1997.
35. Schatzberg A, Posener J, Lindley S, **Belanoff J**, DeBattista C. HPA axis interventions as treatment of depression. 28th Meeting of the International Society of Psychoneuroendocrinology, San Francisco, California, 1997.
36. **Belanoff J**, Glick I. Psychopharmacologic agents on the horizon. American Colleges of Neuropharmacology Annual Meeting, San Juan, Puerto Rico, 1996.

Selected Invited Presentations

1. **Belanoff, J**. Jefferies 2017 Global Healthcare Conference, New York, June 2017
2. **Belanoff, J**. Society of Biological Psychiatry (SOBP), presentation - Symposium: Can the HPA Axis Be Targeted to Treat Depression and Anxiety?- San Diego, May 2017.
3. **Belanoff, J**. Lenox Hill Hospital Grand Rounds, Presentation: - Hypercortisolism (When a Good Hormone Goes Bad) New York, February 2017.
4. **Belanoff, J**. Piper Jaffray 28th Annual Healthcare Conference, New York, November 2016
5. **Belanoff, J**. Cowen and Company 19th Annual Therapeutics Conference, New York,

October 2016

6. **Belanoff, J.** Cantor Fitzgerald 2nd Annual Healthcare Conference, New York, July 2016
7. **Belanoff, J.** Jefferies 2016 Global Healthcare Conference, New York, June 2016
8. **Belanoff J.** Cowen and Company 36th Annual Health Care Conference, Boston, March 2016
9. **Belanoff J.** Piper Jaffray 27th Annual Healthcare Conference, New York, December 2015
10. **Belanoff, J.** FBR 2nd Annual Healthcare Conference, September 9, 2015, Boston, MA
11. **Belanoff, J.** Mt. Sinai Hospital, Adrenal Center, Presentation: - Hypercortisolemia (When a Good Hormone Goes Bad) New York, July 2015
12. **Belanoff, J.** ASCP 2015 Annual Meeting, Presentation – “Mifepristone Plasma Levels and Clinical Response in Patients with Psychotic Depression”, Miami, Florida, June 2015
13. **Belanoff J.** Cowen and Company 35th Annual Health Care Conference, Boston, March 2015
14. **Belanoff J.** University of Florida, Grand Rounds, Presentation: “From Concept to Corcept, The Influence of Aberrant Cortisol Activity on Metabolic, Oncologic and Psychiatric Illnesses”, Gainesville, FL, February 2015
15. **Belanoff J.** Cancer Treatment Centers of America - “Hypercortisolism in Metabolic, Psychiatric and Oncologic Diseases”, Philadelphia, PA, July 2014
16. **Belanoff J.** Janney Capital Markets 1x1 Corporate Access Day, Boston June 2014
17. **Belanoff J.** Ochsner Medical Center, Presentation- “Hypercortisolism in Metabolic, Psychiatric and Oncologic Diseases”, New Orleans, May 2014
18. **Belanoff J.** Cowen and Company 34th Annual Health Care Conference, Boston, March 2014
19. **Belanoff J.** University of Missouri @ Columbia, Grand Rounds, Presentation- Hypercortisolemia (When a Good Hormone Goes Bad) Columbia Missouri, January 2014
20. **Belanoff J.** Oppenheimer 24th Annual Healthcare Conference, New York, December 2013
21. **Belanoff J.** Credit Suisse 2013 Healthcare Conference, Scottsdale, November 2013
22. **Belanoff J.** JMP Securities 8th Annual Securities Healthcare Conference, New York July 2013
23. **Belanoff J.** Janney Capital Markets 1x1 Corporate Access Day, Boston June 2013
24. **Belanoff J.** Deutsche Bank Securities, 38th Annual Health Care Conference, Boston, May 2013
25. **Belanoff J.** Methodist Hospital Research Institute, Presentation – “Depression, Weight Gain and Glucocorticoid Receptor Inhibition”, Houston, April 2013
26. **Belanoff J.** Medical College of Wisconsin, Presentation – “Hypercortisolism in Neuropsychiatric Diseases”, Menomonee Falls, April 2013
27. **Belanoff J.** University of Illinois-Chicago and Rush University Grand Rounds, Presentation – “Hypercortisolemia (When a Good Hormone Goes Bad)”, Chicago, April 2013
28. **Belanoff J.** Johns Hopkins Bayview Medical Campus, Presentation – “From Concept to Corcept” Developing Novel Therapies to Address the Influence of Aberrant Cortisol Activity in Psychiatric and Metabolic Illnesses”, Baltimore, March 2013
29. **Belanoff J.** Cowen and Company 33rd Annual Health Care Conference, Boston, March 2013
30. **Belanoff, J.** AACE, Presentation – “Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing’s Syndrome”, Chicago, February 2013
31. **Belanoff, J.** Endocrine Grand Rounds Conference, Emory University, Atlanta, January 2013
32. **Belanoff, J.** Oppenheimer 23rd Annual Healthcare Conference, New York, December 2012
33. **Belanoff, J.** 42nd Annual ISPNE Conference, New York, September 2012
34. **Belanoff, J.** Stifel Nicolaus 2012 Healthcare Conference, Boston, September 2012

35. **Belanoff, J.** ThinkEquity LLC Ninth Annual Growth Conference:G9, New York, September 2012
36. **Belanoff, J.** JMP Securities 7th Annual Healthcare Conference, New York, July 2012
37. **Belanoff J.** JMP Securities 11th Annual Securities Research Conference, San Francisco, May 2012
38. **Belanoff J.** Bank of America Merrill Lynch Healthcare Conference, Las Vegas, May 2012
39. **Belanoff J.** Cowen and Company 32nd Annual Health Care Conference, Boston, March 2012
40. **Belanoff J.** Citi 2012 Global Health Care Conference, New York, February 2012
41. **Belanoff J.** Credit Suisse Health Care Conference, Arizona, November 2011
42. **Belanoff J.** Stifel Nicolaus Healthcare Conference, Boston, September 2011
43. **Belanoff J.** Stifel Nicolaus Orphan Drug Conference, New York, July 2011
44. **Belanoff J.** Annual Meeting of the American Psychiatric Association, Honolulu, May, 2011
45. **Belanoff J.** Piper Jaffray 22nd Annual Healthcare Conference, New York, December 2010
46. **Belanoff J.** Credit Suisse Healthcare Conference, Arizona, November 2010
47. **Belanoff J.** Lazard Healthcare Conference, New York, November 2010
48. **Belanoff J.** Obesity Society Annual Scientific Meeting, San Diego, October 2010
49. **Belanoff J.** JMP Securities Conference, New York, September 2010
50. **Belanoff J.** UBS Global Sciences Conference, New York, September 2010
51. **Belanoff J.** ISIS (International Society for the Investigation of Stress) 7th World Congress on Stress, Leiden, The Netherlands, August 25 -27, 2010.
52. **Belanoff J.** Stifel Nicolaus Weisel Annual Healthcare Conference, Boston, August, 2010
53. **Belanoff J.** FENS Stress Meeting. Amsterdam, July, 2010
54. **Belanoff J.** The Ninth Annual JMP Securities Research Conference, San Francisco, May 12, 2010.
55. **Belanoff J.** Cowen and Company 30th Annual Health Care Conference. Boston, March 10, 2010.
56. **Belanoff J.** The Oppenheimer 20th Annual Healthcare Conference, November 4, 2009.
57. **Belanoff J.** The JMP Securities Healthcare Focus Conference, October 5, 2009.
58. **Belanoff J.** The Thomas Weisel Partners Annual Healthcare Conference, September 9, 2009.
59. **Belanoff J.** The Rodman & Renshaw 11th Annual Healthcare Conference, September 10, 2009.
60. **Belanoff J.** 40th Annual ISPNE (International Society of Psychoneuroendocrinology Conference), San Francisco CA, July 23-26, 2009.
61. **Belanoff J.** Eighth Annual JMP Securities Research Conference. San Francisco, May 2009.
62. **Belanoff J.** Cowen and Company 29th Annual Healthcare Conference. Boston, March 2009.
63. **Belanoff J.** Rodman & Renshaw 10th Annual Healthcare Conference. New York, November 2008.
64. **Belanoff J.** JMP Securities Third Annual Healthcare Focus Conference, October 2008.
65. **Belanoff J.** Thomas Weisel Partners Annual Healthcare Conference. Boston, September 2008.
66. **Belanoff J.** 39th Annual Meeting of the International Society of Psychoneuroendocrinology (ISPNE) in Dresden, Germany, July 2008.
67. **Belanoff J.** An update on Mifepristone in Psychotic Depression. For: CINP Congress, Munich, Germany, July 2008.
68. **Belanoff J.** The Mitigation of Olanzapine Induced Weight Gain and Metabolic Disturbances with Mifepristone. For: 48th Annual NCDEU Meeting (New Clinical Drug Evaluation Unit) in Phoenix, Arizona, May 2008.
69. **Belanoff J.** Corcept's clinical and corporate progress. For: Rodman & Renshaw 5th Annual Global Healthcare Conference in Monte Carlo, Monaco, May 2008.
70. **Belanoff J.** Mississippi Psychiatric Association Annual Meeting. February 2008.
71. **Belanoff J.** 41st Winter Conference on Brain Research. Snowbird, Utah, January 2008.

72. **Belanoff J.** Potential New Uses for Mifepristone. For: 31st Annual Aldosterone Conference, June 2005.
73. **Belanoff J.** From stress concept to medication of stress system disorder: focus on psychotic major depression. For: Leiden University, Honours Programme 2003, Netherlands.
74. **Belanoff J.** Mifepristone for Psychotic Major Depression. For: CINP Congress, Paris, France 2004.
75. **Belanoff J.** Corlux (Mifepristone) for Psychotic Major Depression. For: Annual Meeting of the Society of Biological Psychiatry, New York, 2004.
76. **Belanoff J.** Clinical Trials of Mifepristone for Psychotic Major Depression (PMD). For: NCDEU, Boca Raton, Florida 2003.
77. **Belanoff J.** A Novel Treatment for Psychotic Major Depression. For: International Society of Psychoneuroendocrinology Annual Meeting, Pisa, Italy 2003.
78. **Belanoff J.** Rapid Reversal of Psychotic Major Depression Using C-1073 (Mifepristone). For: American College of Neuropsychopharmacology Annual Meeting, Waikoloa, Hawaii 2001.
79. **Belanoff J.** Mifepristone: Phase II AD Trial. For: Institute for the Study of Aging, Second Annual Investigators' Meeting, Rye Brook, New York 2001.
80. **Belanoff J.** Mifepristone: Phase II AD Trial. For: Institute for the Study of Aging, Second Annual Investigators' Meeting, Rye Brook, New York 2001.
81. **Belanoff J.** Treatment Advances in Psychotic Depression. For: Grand Rounds, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California 2000.
82. **Belanoff J.** Rapid Reversal of Psychotic Major Depression Using Mifepristone. For: Grand Rounds, Department of Psychiatry, University of Newcastle, Newcastle, United Kingdom 2000.
83. **Belanoff J.** Glucocorticoid Antagonists. For: World Congress of Neuroendocrinology, Rhodes, Greece 2000.
84. **Belanoff J.** HIV, cortisol and cognition. For: International Society of Psychoneuroendocrinology Annual Meeting, Orlando, Florida 1999.
85. **Belanoff J.** Recognizing and treating depression in Ob-Gyn practice. For: Grand Rounds, Department of Obstetrics & Gynecology, Santa Clara Valley Medical Center, San Jose, California 1998.

Electronic Acknowledgement Receipt

EFS ID:	31249170
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	James Fox
Filer Authorized By:	
Attorney Docket Number:	085178-1053027-011410US
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Arguments/Remarks Made in an Amendment	Concomitant_600mg__NF_Res p_due_1_20_18.pdf	547448 <small>c598fe175fdb091681ba0e66016a1dad72641502</small>	no	15

Warnings:

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2	Affidavit-traversing rejections or objections rule 132	Belanoff_Declaration_re_15627359.pdf	3140626	no	4
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Warnings:

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a 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 Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION
OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Examiner: Chris E. SIMMONS

Art Unit: 1629

Confirmation No.: 2957

Att’y Docket: 085178-1053027-011410US

**AMENDMENT and RESPONSE TO NON-FINAL OFFICE ACTION
UNDER 37 C.F.R. § 1.111**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450

Dear Commissioner:

“TrackOne” status for this application was granted by the USPTO on August 11, 2017. Accordingly, this application is being examined according to “Prioritized Examination” procedures.

This Amendment and Response is in response to the Non-Final Office action mailed October 20, 2017, and is timely filed within three months of that mailing date.

An Information Disclosure Statement accompanies this Amendment and Response.

Amendments to the Claims begin on page 2.

Remarks begin on page 5.

Amendments to the Claims

This listing of claims replaces all versions, and listings, of the claims in this application.

Claim Listing

1. (currently amended) A method of treating Cushing's syndrome in a patient who is taking a once-daily (OD) dose of a glucocorticoid receptor antagonist (GRA), said OD dose having an original OD dose amount of said GRA, comprising reducing the daily amount of the OD dose of said GRA from ~~an~~ said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA.

2. (currently amended) The method of claim 1, wherein ~~said original dose is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA~~ is mifepristone, and said ~~adjusted dose is 600 mg per day of said GRA~~ CYP3A inhibitor is a strong CYP3A inhibitor.

3. (currently amended) The method of claim 1, wherein ~~said original dose is 600 milligrams (mg) per day of said GRA,~~ and said adjusted OD dose is 600 300 mg per day of said GRA, ~~further comprising after upwardly titrating the adjusted OD dose amount from 300 mg per day up to a maximum of 600 mg per day of said GRA.~~

4. (currently amended) The method of claim ~~4~~ 3, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.

5. (currently amended) The method of claim ~~2~~ 1, wherein said GRA is mifepristone and said CYP3A inhibitor is ~~a strong CYP3A inhibitor~~ selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

6. (currently amended) The method of claim 3, wherein said GRA is mifepristone and said CYP3A inhibitor is ~~a strong CYP3A inhibitor~~ selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

7. (original) The method of claim 1, wherein said CYP3A inhibitor is ketoconazole.

8. (original) The method of claim 4, wherein said CYP3A inhibitor is ketoconazole.

9. (currently amended) The method of claim ~~5~~ 2, wherein said CYP3A inhibitor is ketoconazole.

10. (currently amended) A method of treating symptoms associated with elevated cortisol levels in a patient who is taking a once-daily (OD) dose of a glucocorticoid receptor antagonist (GRA), said OD dose having an original OD dose amount of said GRA, comprising reducing the daily amount of the OD

Response to Non-Final Office action
U.S. Patent Application 15/627,359

dose of said GRA from ~~an~~ said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA.

11. (currently amended) The method of claim 10, wherein ~~said original dose is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA~~ is mifepristone, and ~~said adjusted dose of GRA is 600 mg per day of said GRA~~ CYP3A inhibitor is a strong CYP3A inhibitor.

12. (currently amended) The method of claim 10, wherein ~~said original dose is 600 milligrams (mg) of per day of said GRA, and~~ said adjusted OD dose amount is 600 300 mg per day of said GRA, further comprising after upwardly titrating the adjusted OD dose amount from 300 mg per day up to a maximum of 600 mg per day of said GRA.

13. (currently amended) The method of claim ~~40~~ 12, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.

14. (currently amended) The method of claim ~~44~~ 10, wherein said GRA is mifepristone and said CYP3A inhibitor is ~~a strong CYP3A inhibitor~~ selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

15. (currently amended) The method of claim 12, wherein said GRA is mifepristone and said CYP3A inhibitor is ~~a strong CYP3A inhibitor~~ selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

16. (currently amended) The method of claim 10, wherein said CYP3A inhibitor is ketoconazole.

17. (currently amended) The method of claim 13, wherein said CYP3A inhibitor is ketoconazole.

18. (currently amended) The method of claim ~~44~~ 11, wherein said CYP3A inhibitor is ketoconazole.

19. (currently amended) A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking a once-daily (OD) dose of a glucocorticoid receptor antagonist (GRA), said OD dose having an original OD dose amount of said GRA, comprising reducing the daily amount of the OD dose of said GRA from an said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is

selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA.

20. (currently amended) The method of claim 19, wherein ~~said original dose is selected from 900 milligrams (mg) and 1200 mg per day of said GRA~~ is mifepristone, and ~~said adjusted dose of GRA is 600 mg per day of said GRA~~ CYP3A inhibitor is a strong CYP3A inhibitor.

21. (currently amended) The method of claim 19, wherein ~~said original dose is 600 milligrams (mg) per day of said GRA, and said adjusted OD dose is 600 300 mg per day of said GRA,~~ further comprising after upwardly titrating the adjusted OD dose amount from 300 mg per day up to a maximum of 600 mg per day of said GRA.

22. (currently amended) The method of claim ~~19~~ 21, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor.

23. (currently amended) The method of claim ~~20~~ 19, wherein said GRA is mifepristone and said CYP3A inhibitor is ~~a strong CYP3A inhibitor~~ selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

24. (currently amended) The method of claim 21, wherein said GRA is mifepristone and said CYP3A inhibitor is ~~a strong CYP3A inhibitor~~ selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

25. (original) The method of claim 19, wherein said CYP3A inhibitor is ketoconazole.

26. (original) The method of claim 22, wherein said CYP3A inhibitor is ketoconazole.

27. (currently amended) The method of claim ~~23~~ 20, wherein said CYP3A inhibitor is ketoconazole.

28. (currently amended) A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein said patient is taking a once-daily (OD) dose of mifepristone, said OD dose having an OD dose amount of 900 milligrams (mg) or 1200 mg mifepristone, comprising reducing the OD amount of mifepristone to provide a reduced OD dose of 600 milligrams (mg) mifepristone, and administering a daily said reduced OD dose of 600 milligrams (mg) mifepristone when the patient is receiving concomitant administration of a CYP3A inhibitor.

29. (original) The method of claim 28, wherein said CYP3A inhibitor is ketoconazole.

30. (currently amended) The method of claim 29, wherein said daily reduced OD dose of 600 mg mifepristone per day is titrated up to 600 mg mifepristone per day ~~from~~ at least two days after administering at least two reduced OD doses of 300 mg mifepristone per day.

REMARKS

The In-Person Interview

Applicant thanks the Examiner for his time and consideration in meeting with inventor Dr. Joseph Belanoff and with Applicant's attorney on December 7, 2017, and for discussing the claims, references, and the obviousness rejections.

The Information Disclosure Forms

Applicant acknowledges the review and consideration of the references cited in the Information Disclosure (IDS) forms submitted on June 19, 2017 and on October 3, 2017. Applicant notes that an IDS form was also filed on November 1, and that Applicant files a further IDS form herewith. Applicant respectfully requests that the USPTO consider the references cited therein.

The Claims

Claims 1-6, 9-24, 27, 28, and 30 stand amended to more particularly point out and distinctly claim subject matter Applicant wishes to claim in the present application.

Support for the claim amendments is found, for example, in the original claims as filed; at page 2, paragraph [0007]; at pages 4-5, paragraph [0016]; at pages 6-8, paragraphs [0020]-[0023]; at pages 12-15, paragraphs [0036]-[0040]; at page 23, paragraph [0068]; at page 46, paragraphs [00157]-[00158]; at page 74, paragraph [00255]; at pages 80-81, paragraph [00280]; and elsewhere in the application as originally filed.

No new matter is added by way of the claim amendments.

Claims 1-30 were examined, and stand rejected.

The Rejections Under 35 U.S.C. § 112(b)

Claims 1, 10, and 19 stand rejected under 35 U.S.C. § 112(b) for alleged lack of antecedent basis for the term "the daily dose" (pages 2 - 3 of the instant Office action).

Without acquiescence to any rejection, the claims now stand amended to provide explicit antecedent basis for the term "the daily dose" (now amended to "once-daily (OD) dose" for greater clarity) and are believed to have proper antecedent basis and to make clear that the GRA is administered once a day.

Accordingly, proper antecedent basis is believed to be provided for these terms and the rejections of claims 1, 10, and 19 under 35 U.S.C. § 112(b) are believed to be overcome.

The Rejections Under 35 U.S.C. § 103

Claims 1-30 stand rejected under 35 U.S.C. § 103 for alleged obviousness over Korlym[®] (mifepristone) [package insert] (hereafter "package insert") in view of Ulmann (US 2010/0261693 (hereafter "Ulmann")) (pages 3-8 of the instant Office action).

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Obviousness under 35 U.S.C. §103 is determined with respect to the subject matter as a whole, and requires that each and every element of the claimed invention is provided by the combination of the cited references, as set forth by the U.S. Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), and as re-affirmed in *KSR International Company v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). The factors articulated by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) to be considered in an obviousness inquiry under 35 U.S.C. §103 include: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness.

In addition to the requirement that all the claim limitations be taught or suggested by the prior art references, a *prima facie* case of obviousness requires *i*) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; and *ii*) a reasonable expectation of success for the combination. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and may not be based on the applicant's disclosure. In *re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully traverses the rejections of claims 1-30 under 35 U.S.C. § 103.

The Claimed Invention

CYP3A enzymes are a major factor in the metabolism of many drugs, including GRAs such as mifepristone. Inhibition of CYP3A activity when a patient is receiving a drug that is metabolized by CYP3A enzymes can greatly reduce metabolism of that drug, leading to excessively high or toxic levels of the drug. As discussed in greater detail below, CYP3A inhibitors can greatly increase the levels of other drugs given concomitantly (e.g., by 6.5-fold to more than 14-fold (Greenblatt et al.)). As stated by Dr. Belanoff in his Declaration (attached), those of skill in the art expected that "ketoconazole would increase mifepristone levels by 4 to 5 times" when given with a CYP3a inhibitor such as ketoconazole. This expectation was reflected in the FDA label for Korlym[®] which stated that mifepristone should be used in combination with strong CYP3A inhibitors "only when necessary, and that in such cases the dose should be limited to 300 mg per day" (see, e.g., the Korlym[®] label, and page 5 of the instant Office action).

Surprisingly, in contrast to the expectation that a GRA level would be greatly increased by concomitant administration of a CYP3A inhibitor, Applicant has discovered that this expectation in the art was incorrect, and that GRAs and CYP3A inhibitors may be safely administered together according to the present methods.

See, for example, Examples 1, 2, and 3, and the Tables at pages 74 – 87, and 93 - 96. As disclosed in Table 3 of the present application (page 95), 600 mg per day mifepristone administered with ketoconazole (400 mg total, given twice daily) gave the following small increases in mifepristone levels (about 28% –

38%):

Analyte	Parameter	N	Ratio%		
			Test/Reference	Lower 90% CI	Upper 90% CI
Mifepristone	C _{max}	13	127.59	116.66	139.54
	AUC ₀₋₂₄	13	138.01	127.12	149.84

Present claims 1 - 27 are directed to methods of treating Cushing's syndrome, methods of treating a symptom associated with Cushing's syndrome, and methods of controlling hyperglycemia secondary to hypercortisolism in a patient taking an original once-daily (OD) dose amount of a glucocorticoid receptor antagonist (GRA) by:

reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA (see, e.g., claims 1, 10, and 19);

and, in some of the dependent claims, by:

wherein said adjusted OD dose is 600 mg per day of said GRA after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of said GRA (e.g., claims 3, 12 and 21).

Per some dependent claims, the GRA may be mifepristone, and the CYP3A inhibitor may be selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole; may be a strong CYP3A inhibitor; and, in particular, may be ketoconazole.

Claims 28 – 30 also require a reduction in an original once-daily dose (from 900 mg/day or 1200 mg/day to 600 mg/day) of the GRA mifepristone. The CYP3A inhibitor is specified as ketoconazole in dependent claim 29. Dependent claim 30 requires upwardly titrating the adjusted OD dose amount up to 600 mg mifepristone per day (at least two days following OD administration of at least two OD doses of 300 mg/day).

Thus, all claims require at least 33% *reduction* of an original once-daily GRA dose of 1200 mg per day or 900 mg per day, and some claims further require titrating the once-daily GRA dose upwardly from 300 mg to 600 mg, when the patient is receiving concomitant administration of CYP3A inhibitor.

As discussed in greater detail in the following, the cited references Korlym[®] package insert and Ulmann, and their combination, lack at least the required step of reducing an original once-daily mifepristone dose by at least 33% when the patient is receiving concomitant administration of a CYP3A

inhibitor; the cited references and their combination lack at least the required step of reducing an original once-daily mifepristone dose of 1200 mg or 900 mg per day to a dose of 600 mg per day when the patient is receiving concomitant administration of a CYP3A inhibitor; and the cited references and their combination further lack titrating a reduced once-daily dose up to 600 mg per day when the patient is receiving concomitant administration of a CYP3A inhibitor. Moreover, the cited references and their combination lacks any suggestion or motivation to provide these or other elements missing from the references, nor, in view of these references, would one of skill in the art have any reasonable expectation of success for the claimed methods.

In the following, since the cited references refer to mifepristone, reference is made to the GRA mifepristone; it will be understood that references to mifepristone may also apply generally to glucocorticoid receptor antagonists (GRAs), and is not necessarily be limited to mifepristone alone unless the context (e.g., a quote from the Korlym[®] package insert that uses the term “mifepristone”) makes clear that the reference is to the compound mifepristone itself, and not as a representative GRA.

CYP3A Inhibitors

Many GRAs, such as mifepristone, are metabolized by CYP3A enzymes. Thus, it would be expected that drugs that inhibit CYP3A enzymes would inhibit metabolism of such GRAs, and so lead to increased plasma levels of those GRAs due to reduced metabolic degradation of the GRAs. One useful measure of drug levels in plasma is the “area under the curve” termed AUC.

Such concern is borne out by published clinical studies and by clinical experience. For example, Applicant draws the attention of the USPTO to Greenblatt et al. (Brit. J. Clin. Pharmacol. **80(3)**:342-350 (2015)) which reports that representative CYP3A inhibitors increased AUC by more than 11-fold (ketoconazole); more than 7-fold (itraconazole); more than 6-fold (clarithromycin); and more than 14-fold (ritonavir). Thus, CYP3A inhibitors typically have a very large effect on AUC.

The Food and Drug Administration (FDA) notes that “Patients frequently use more than one medication at a time. Unanticipated, unrecognized, or mismanaged DDIs [drug-drug interactions] are an important cause of morbidity and mortality associated with prescription drug use” (page 2 of “Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications Guidance for Industry”). Regarding such DDIs, Applicant reproduces below relevant portions of a table from the FDA reference “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers”

Table 3-2: Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A	boceprevir, cobicistat ^(a) , conivaptan ^(b) , danoprevir and ritonavir ^(c) , elvitegravir and ritonavir ^(c) , grapefruit juice ^(k) , indinavir and ritonavir ^(c) ,	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone ^(h) , erythromycin, fluconazole ^(l) , fluvoxamine ^(e) ,	chlorzoxazone, cilostazol, fosaprepitant, isradefylline, ivacaftor ⁽ⁱ⁾ , lomitapide, ranitidine, ranolazine ^(j) , tacrolimus, ticagrelor ^(f)

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	itraconazole ^(b) , ketoconazole, lopinavir and ritonavir ^(b,d) , paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) ^(d) , posaconazole, ritonavir(h,j), saquinavir and ritonavir ^(b,d) , telaprevir ^(b) , tipranavir and ritonavir ^(b,d) , troleandomycin, voriconazole	imatinib, fosfopam, verapamil ^(b)	
	clarithromycin ^(b) , diltiazem ^(b) , idelalisib, nefazodone, nelfinavir ^(b)		

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5 -fold, ≥ 2 to < 5 -fold, and ≥ 1.25 to < 2 -fold, respectively. Strong inhibitors of CYP3A causing ≥ 10 -fold increase in AUC of sensitive index substrate(s) are shown above the dashed line.

This table is prepared to provide examples of clinical inhibitors and is not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

^(b) Strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A.

^(d) Strong inhibitors of CYP2C19 and CYP2D6.

^(j) Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥ 1.25 -fold).

^(h) Strong inhibitors of CYP3A and weak inhibitor of CYP2D6.

^(k) Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

^(l) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

Applicant notes that the FDA labels as "strong" inhibitors those compounds that increase AUC by 5-fold or greater; many (those above the "dashed" line) increase AUC by 10-fold or more (emphasis added). Thus, the FDA promulgates information to those of skill in the art which indicates that CYP3A inhibitors can be expected to produce large increases in AUC of other drugs when the CYP3A inhibitor is given concomitantly with drugs metabolized by the CYP3A system.

In addition, as discussed below (following the discussion of the cited references), Applicant provides herewith an Expert Declaration further supporting the teaching of the references cited above to the effect that those of skill in the art expected that concomitant administration of a GRA with CYP3A inhibitors (particularly strong CYP3A inhibitors) would lead to very large increases in the AUC of GRAs. Thus, the teaching and expectation in the art was that CYP3A inhibitors, particularly strong CYP3A inhibitors, could greatly increase levels of other drugs administered concomitantly with the CYP3A inhibitors.

The Korlym[®] Package Insert

The USPTO acknowledges that the Korlym[®] package insert ("package insert") a) teaches a maximum mifepristone dose of 300 mg per day when used with strong CYP3A inhibitors, and that it b) further lacks teaching to reduce an original mifepristone dose by at least 33% (page 5 of the instant Office action). The package insert also lacks any suggestion, and, by explicitly limiting the dose to 300 mg per day, teaches away from, titrating the mifepristone dose up from 300 mg per day to 600 mg per day when used

with strong CYP3A inhibitors.

As noted by the USPTO, the package insert teaches that mifepristone should be used with extreme caution in patients taking ketoconazole and other strong inhibitors of CYP3A, and further teaches that mifepristone should be used in combination with strong CYP3A inhibitors “only when necessary, and that in such cases the dose should be limited to 300 mg per day” (see page 5 of the instant Office action). Thus, those of skill in the art are taught by the package insert to avoid use of mifepristone with CYP3A inhibitors, and, if such concomitant administration with CYP3A inhibitors is necessary, **to limit the dose of mifepristone to 300 mg per day**. Thus, any administration of more than 300 mg mifepristone along with a CYP3A inhibitor is forbidden by the FDA label, and thus, for at least this reason, safe administration of more than 300 mg mifepristone along with a CYP3A inhibitor would have been considered surprising by those of skill in the art.

The package insert warns that “Korlym[®] should be used with extreme caution in patients taking ketoconazole and other strong inhibitors” and that “Mifepristone should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 300 mg per day” (part 5.6). Thus, the package insert teaches that the maximum dose of the GRA mifepristone should be no more than 300 mg per day when used with strong CYP3A inhibitors. Applicant notes that 600 mg/day is greater than the 300 mg/day limit taught by the package insert. Thus, the package insert explicitly teaches away from administering 600 mg per day doses of mifepristone, as recited in the present claims.

In addition to requiring **limiting** the mifepristone dose to 300 mg (emphasis added) for “patients taking ketoconazole and other strong inhibitors”, the package insert fails to discuss reducing the mifepristone dose by 33% when patients taking mifepristone begin taking a strong CYP3A inhibitor such as ketoconazole as well. The package insert also lacks any teaching to reduce the mifepristone dose by at least 33% when a patient taking mifepristone later begins taking a strong CYP3A inhibitor. Moreover, the package insert lacks any teaching to titrate that daily amount back up to 600 mg/day after reducing the dosage by at least 33%.

Thus, in addition to 1) teaching away from 600 mg per day doses of mifepristone when concomitantly administering a strong CYP3A inhibitor, the package insert also 2) lacks teaching of reducing a GRA dose by at least 33%, and 3) teaches away from upwardly titrating a GRA dose when used with strong CYP3A inhibitors.

Ulmann

Ulmann is presented as suggesting “that mifepristone and an inhibitor of cortisol synthesis such as ketoconazole, mitotane, metyrapone, aminoglutethimide, or fluconazole may be used to treat Cushing syndrome” (page 6 of the instant Office action).

Ulmann teaches “However in a long term, such high dosage of mifepristone given with long

intervals between doses (e.g. once a day) triggers a massive secretion of cortisol due to interruption of the endogenous feedback mechanism. This high level of cortisol then overwhelms the blockage of the glucocorticoid receptors, leading to hypercortisolism (Raux-Demay et al, 1990).” (paragraph [0008], page 1 of Ulmann).

Ulmann teaches “In order to avoid secretion of cortisol in response to the blockade of the glucocorticoid receptor, it is now proposed to give multiple low doses or a sustained-release low dosage of glucocorticoid receptor antagonist, and/or to combine the glucocorticoid receptor antagonist with an inhibitor of cortisol synthesis, for treating Cushing's syndrome.” (paragraph [0009], page 1 of Ulmann). Ulmann further teaches that “multiple low doses” of a GRA may be “at least twice per day” (e.g., paragraphs [0010], [0011], and [0037]); “at least three times per day, e.g., three or four times a day” (paragraph [0038], page 3).

Thus, Ulmann explicitly teaches away from **once-a-day** dosing of mifepristone, warning that once-a day dosing “triggers a massive secretion of cortisol ...leading to hypercortisolism” (paragraph [0008] of Ulmann). Since Cushing’s syndrome is characterized by hypercortisolism, Ulmann clearly teaches NOT to administer mifepristone once per day when attempting to treat Cushing’s syndrome; instead, Ulmann teaches the need to use “multiple low doses” of glucocorticoid receptor antagonist to treat Cushing’s syndrome (paragraph [0009]; at least twice a day (paragraphs [0010], [0011], and [0037]); at least three times a day, e.g., three or four times a day (paragraph [0038]). (Applicant notes that the “sustained release” suggested by Ulmann in the passage cited above is a form of multiple dosing, releasing drugs continuously or intermittently over a long period of time, and is not once-per-day dosing; see, e.g., the definition in Goodman and Gilman: “the so-called controlled-release, timed-release, sustained-release, or prolonged-action pharmaceutical preparations that are designed to produce slow, uniform absorption of the drug for 8 hours or longer” (Goodman and Gilman, Eighth Edition, 1990, Chapter 1, page 7).)

Moreover, Ulmann teaches the same GRA doses for GRAs administered with, and GRAs administered without, cortisol synthesis inhibitors. Regarding both a) at least twice a day administration of a GRA alone (paragraph [0041], page 4,) and b) administration of a GRA along with a cortisol synthesis inhibitor (paragraph [0055], page 4,), Ulmann teaches the same amounts, stating that the “total daily amount of the glucocorticoid receptor antagonist administered may be advantageously inferior or equal to 800mg, preferably inferior or equal to 600mg, still preferably inferior or equal to 400mg, still more preferably inferior or equal to 300mg”. Thus, in contrast to the present claims, Ulmann teaches *no* dose adjustment when mifepristone is used with cortisol synthesis inhibitors such as ketoconazole. Ulmann fails to discuss **any** actions to be taken when a GRA such as mifepristone and a cortisol synthesis inhibitor such as, e.g., ketoconazole, are concomitantly administered that differ from those to be taken when a glucocorticoid receptor antagonist is administered alone.

Thus, Ulmann lacks any discussion of **adjusting a mifepristone dose** when a patient is receiving

concomitant administration of an inhibitor of cortisol synthesis. In particular, Ulmann does not discuss **reducing a once-daily mifepristone dose** when a patient is receiving concomitant administration of an inhibitor of cortisol synthesis. Instead, by teaching that the doses are the same with and without a cortisol synthesis inhibitor, Ulmann instead teaches that there should be **no such adjustment**. This is contrary to the requirements of the present claims.

In summary, Ulmann teaches that once-daily doses trigger a “massive secretion of cortisol” so that multiple daily doses are required to avoid hypercortisolism; fails to teach reducing an original dose of mifepristone by at least 33% when a patient receiving mifepristone is also receiving concomitant administration of a CYP3A inhibitor; and fails to teach reducing an original once-daily dose of 1200 mg per day or 900 mg per day mifepristone to a once-daily dose of 600 mg per day mifepristone when a patient receiving mifepristone is also receiving concomitant administration of a CYP3A inhibitor.

The Combination of the Package Insert with Ulmann

As discussed above, the Korlym[®] package insert forbids greater than 300 mg per day of mifepristone when used in combination with strong CYP3A inhibitors; lacks any teaching to reduce an original once-daily mifepristone dose by at least 33% to provide an adjusted mifepristone dose; and lacks any teaching of reducing once-daily doses of 1200 mg per day or 900 mg per day of mifepristone to 600 mg mifepristone once-daily; and lacks any teaching of upwardly titrating a reduced once-daily dose of mifepristone to 600 mg following administration of an adjusted mifepristone dose (in particular, for claim 30, at an interval of at least two days).

As discussed above, Ulmann teaches away from once per day administration; teaches away from adjusting a mifepristone dose when administered with a cortisol synthesis inhibitor; lacks any teaching of reducing a once-daily mifepristone dose by at least 33% when mifepristone is receiving concomitant administration of a CYP3A inhibitor selected from the list recited in the claims; and lacks any teaching of reducing a 1200 mg or 900 mg once-daily mifepristone dose to once-daily 600 mg mifepristone when the patient is receiving concomitant administration of a CYP3A inhibitor selected from the list recited in the claims.

Thus, the combination of the package insert with Ulmann lacks suggestion of, and teaches away from, reducing an original once-daily mifepristone dose by at least 33%; however, this is required by the present claims. More particularly, the combination of the package insert with Ulmann also lacks suggestion of, and teaches away from, reducing an original once-daily mifepristone dose by at least 33%, where the original once-daily dose is 1200 mg or 900 mg mifepristone, and the adjusted OD dose is 600 mg mifepristone; however, this is required by present claims.

The combination of the package insert with Ulmann also lacks suggestion of, and teaches away from, reducing an original once-daily mifepristone dose by at least 33% from 1200 mg or 900 mg per day to

a once-daily dose of 600 mg per day, where the 600 mg once-daily dose was upwardly titrated from 300 mg once-daily dose to a once-daily dose of 600 mg mifepristone; however, this is required by present claims 3, 12, 21, and 30.

In view of the teaching of the cited references, which expressly forbid or teach away from required elements of the claimed methods, those of skill in the art would have no motivation to combine those references, and would have no motivation to attempt to provide the claimed invention.

For the same reasons (including, e.g., that Ulmann teaches that once per day administration causes hypercortisolism; that the package insert warns against administering greater than 300 mg mifepristone when the patient is also receiving a strong CYP3A inhibitor), those of skill in the art would have no reasonable expectation of success for the claimed invention; instead, those of skill in the art, in view of the combined teachings of the cited references, would not expect the claimed methods to be successful.

Thus, even when combined, the cited references lack elements required by the present claims, teach away from required claim elements, provide no suggestion or motivation to provide the missing elements, and provide no reasonable expectation of success for the claimed methods.

The Expert Declaration

Applicant submits herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Joseph Belanoff, the inventor, practicing psychiatrist, and Chief Executive Officer of the assignee, Corcept Therapeutics, whose primary mission is to provide improved medicine for a variety of illnesses based on targeting glucocorticoid signaling. Regarding co-administration of mifepristone and a strong CYP3A inhibitor, in his Declaration Dr. Belanoff states that “The belief in the art, as forcefully indicated by the warning the FDA required in the Korlym® package insert, was that such co-administration would be dangerous. The FDA warning stated that mifepristone should be limited to 300 mg per day if administered with a strong CYP3A inhibitor. It was expected that the CYP3A inhibitor would reduce mifepristone metabolism to such a degree that mifepristone concentrations would be dangerously high if administered with a CYP3A inhibitor.” (point 6 of the Belanoff Declaration) and that “The expectation was that ketoconazole would increase mifepristone levels by 4 to 5 times” (point 8).

However, surprisingly, “Instead, the increase in mifepristone levels caused by ketoconazole was 0.3 times. We also surprisingly found that such co-administration was manageable, and allowed for safe methods of treatment with both drugs. By reducing the mifepristone dose by 33% when administering a CYP3A inhibitor such as ketoconazole, the mifepristone concentration remained within safe, and effective, levels. It was further surprisingly found that in some cases, the mifepristone dose could be titrated upwardly, after the initial reduction, to provide effective treatment while mifepristone levels remained within safe bounds.” (point 8).

Dr. Belanoff states (point 12 of the Belanoff Declaration) “those of skill in the art, including the

FDA, expected that the combination of mifepristone and ketoconazole might result in excessive mifepristone levels, which might be dangerous or therapeutically counterproductive. Ulmann provides no method to avoid this possible deleterious outcome; instead, Ulmann suggests multiple doses per day, in order to avoid excess cortisol levels. Even if one were to follow Ulmann, one would not be led to the present methods which require once per day administration of mifepristone, where the amount of mifepristone is reduced by at least 33% from the dose administered in the absence of a CYP3A inhibitor. Thus, Ulmann provides no suggestion to those of skill in the art that solves the possible problems of combining mifepristone with ketoconazole, and does not suggest the present methods.” Dr. Belanoff further notes that “those of skill in the art would have found the methods now claimed, and the results of the practice of those methods, to be surprising and unexpected” (point 13).

Accordingly, in view of the teaching of the cited references, those of skill in the art not be provided with all required elements, would be led away from attempting to combine those references, would be taught away from the claimed invention, and would find the present results and methods surprising and unexpected.

Surprising and Unexpected Results

To reiterate, the present application provides the surprising results that subjects may be safely administered a once-daily adjusted dose of 600 mg of a GRA along with a strong CYP3A inhibitor (see Examples 1, 2, and 3, and the Tables). These results are surprising for at least the reason that the FDA, in approving the use of mifepristone to treat hyperglycemia secondary to hypercortisolism in patients with endogenous Cushing’s syndrome, stated in the “*Warnings and Precautions*” section of the Korlym[®] label that concomitant use of mifepristone with strong CYP3A inhibitors should be “only when necessary and limit mifepristone dose to **300 mg**”. These results are also surprising for at least the reason that Ulmann teaches that once-daily dosing of mifepristone “triggers massive secretion of cortisol”, and also teaches the use of the same GRA amounts – *no* dose adjustment - whether or not the GRA is administered with a cortisol synthesis inhibitor.

Applicant again notes that CYP3A inhibitors typically have a very large effect on AUC (see, e.g., Greenblatt et al., which reports that representative CYP3A inhibitors increased AUC by more than 11-fold (ketoconazole); 7-fold (itraconazole); 6-fold (clarithromycin); and 14-fold (ritonavir)).

Summarizing some of the points made by Dr. Belanoff in his Declaration, it was: expected that the combination of mifepristone and ketoconazole would increase mifepristone levels by 4 to 5 times (point 8) which would be dangerously high (point 6); or therapeutically counterproductive (point 12). However, surprisingly, the increase in mifepristone levels caused by ketoconazole was 0.3 times (point 8) which those of skill in the art would have found to be surprising and unexpected (point 13).

The present claims, based on these surprising results, provide surprising and improved methods for treating Cushing’s syndrome patients treated with GRA and a CYP3A inhibitor. These methods were not

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15627359
	Filing Date	2017-06-19
	First Named Inventor	Joseph K. Belanoff
	Art Unit	1629
	Examiner Name	Chris E. SIMMONS
	Attorney Docket Number	085178-1053027-011410US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15627359
	Filing Date	2017-06-19
	First Named Inventor	Joseph K. Belanoff
	Art Unit	1629
	Examiner Name	Chris E. SIMMONS
	Attorney Docket Number	085178-1053027-011410US

1	Greenblatt et al. "Ritonavir is the best alternative to ketoconazole as an index inhibitor of cytochrome P450-3A in drug-drug interaction studies," Brit. J. Clin. Pharmacol. 80(3):342-350 (2015))
2	"Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications Guidance for Industry" dated October 2017 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093606.htm (accessed December 11, 2017)
3	"Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (FDA website (cached), accessed December 8, 2017)
4	Chapter 1, "Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination", Benet LZ et al., in The Pharmacological Basis of Therapeutics, Eighth Edition, Pergamon Press, Elmsford, New York, USA, 1990, pages 3-32
5	U.S. 15/627,368, final Office action issued December 5, 2017 for U.S. Application entitled "Concomitant Administration of Glucocorticoid Receptor Modulators and CYP3A or Steroidogenesis Inhibitors", filed June 19, 2017; inventor J. Belanoff, Applicant: Corcept Therapeutics; published as US 2017-0281651 A1.

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	<input type="text"/>	Date Considered	<input type="text"/>
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15627359
	Filing Date	2017-06-19
	First Named Inventor	Joseph K. Belanoff
	Art Unit	1629
	Examiner Name	Chris E. SIMMONS
	Attorney Docket Number	085178-1053027-011410US

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.

The 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	/James A. Fox/	Date (YYYY-MM-DD)	2017-12-15
Name/Print	James A. Fox	Registration Number	38455

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 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.**

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

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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.

Electronic Patent Application Fee Transmittal

Application Number:	15627359			
Filing Date:	19-Jun-2017			
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS			
First Named Inventor/Applicant Name:	Joseph K. Belanoff			
Filer:	James Fox			
Attorney Docket Number:	085178-1053027-011410US			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	90	90
Total in USD (\$)				90

Electronic Acknowledgement Receipt

EFS ID:	31249248
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	James Fox
Filer Authorized By:	
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	15-DEC-2017
Filing Date:	19-JUN-2017
Time Stamp:	21:43:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
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RAM confirmation Number	121817INTEFSW21465100
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6	Non Patent Literature	Clinical_DDI_Studies_Guidance_oct_2017.pdf	807064	no	32
			b8981daa4ae62f3a7ca604abdb0cf3118e57d3dd		
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If a new application is being filed and the application includes the necessary components for a 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 Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION
OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A
INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: Chris E. SIMMONS

Technology Center/Art Unit: 1629

INFORMATION DISCLOSURE

STATEMENT

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

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

This IDS is being filed before the mailing date of a final Office Action, Notice of Allowance, or any other action that closes prosecution.

Respectfully submitted,

Dated: December 15, 2017

/James A. Fox/

James A. Fox
Registration No. 38,455

Corcept Therapeutics
149 Commonwealth Drive
Menlo Park, California 94025

Attachment

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 Substitute for Form PTO-875	Application or Docket Number 15/627,359	Filing Date 06/19/2017	<input type="checkbox"/> To be Mailed
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ENTITY: LARGE SMALL MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE <small>(37 CFR 1.16(k), (l), or (m))</small>	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A	
TOTAL CLAIMS <small>(37 CFR 1.16(i))</small>	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	minus 3 =	*	X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	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).			
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>				
* 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)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	12/15/2017	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR			
	Total <small>(37 CFR 1.16(i))</small>	* 30	Minus	** 30	= 0	X \$40 = 0
	Independent <small>(37 CFR 1.16(h))</small>	* 4	Minus	***4	= 0	X \$210 = 0
	<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>					
					TOTAL ADD'L FEE	0

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR			
	Total <small>(37 CFR 1.16(i))</small>	*	Minus	**	=	X \$ =
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>					
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
 *** 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.

LIE
 CAROLYN THOMAS

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.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION
OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Examiner: Chris E. SIMMONS

Art Unit: 1629

Confirmation No.: 2957

Att’y Docket: 085178-1053027-011410US

**SUPPLEMENTAL AMENDMENT
UNDER 37 C.F.R. § 1.111**

Mail Stop **Amendment**

Commissioner for Patents
P.O. Box 1450

Dear Commissioner:

This Supplemental Amendment is in addition to, and supplements, the Amendment and Response regarding the above-named application filed on December 15, 2017. Both this Supplemental Amendment and the Amendment and Response filed on December 15, 2017 are in response to the Non-Final Office action mailed October 20, 2017, and both are timely filed on or before the first business day after the date that is three months from that mailing date.

A Second Declaration by Dr. Joseph K. Belanoff accompanies this Supplemental Amendment.

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

Remarks begin on page **3**.

Amendments to the Specification

Please amend the specification at page 67, paragraph [00223] as follows:

[00223] Accordingly, in embodiments disclosed herein, the compositions include pharmaceutical compositions including a pharmaceutically acceptable carrier or excipient, a glucocorticoid receptor antagonist (GRA), and a SI. SIs include, for example, ketoconazole, levoketoconazole, metyrapone, ~~LCI699~~, aminoglutethimide, etomidate, LCI699 (Osilodrostat), and others.

Please amend the specification at page 86, paragraph [00302] as follows:

[00302] The results presented in this example indicate that, with inhibition of CYP3A (e.g., by co-administration of a strong CYP3A inhibitor such as ketoconazole), a subject ~~previously~~ administered ~~1200~~ 900 mg mifepristone daily would experience corresponding increases in mifepristone C_{max} and AUC of 27.59% and of 38.01%, respectively, which should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily. Thus, the results of these measurements indicate that a subject, previously receiving a dose of 1200 mg mifepristone daily, may be safely administered a dose of 900 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen. Similarly, the results of these measurements indicate that a subject, previously receiving a dose of 900 mg mifepristone daily, may be safely administered a dose of 600 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen. In addition, the results of these measurements indicate that a subject, previously receiving a dose of 600 mg mifepristone daily, may be safely administered a dose of 300 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen.

REMARKS

The Specification

Paragraph [00223] on page 67 stands amended to correct a typographical error (duplication of “LCI699”).

Paragraph [00302] on page 86 stands amended to correct typographical errors (delete “previously” and replace “1200” by “900” as indicated).

Support for the amendments to the specification is found, for example, in the application as originally filed, for example, at page 84, paragraph [00295], which states:

“The value of 87% for GMR of the AUCs suggests that 900 mg mifepristone in the presence of ketoconazole would better match the exposure of a subject to 1200 mg mifepristone alone than would 600 mg mifepristone in the presence of ketoconazole. Thus, these data also support the use of 900 mg mifepristone, and higher doses as well, in the presence of ketoconazole.”;

and within the corrected paragraph itself, at page 86, paragraph [00302], which states:

“Thus, the results of these measurements indicate that a subject, previously receiving a dose of 1200 mg mifepristone daily, may be safely administered a dose of 900 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen.”;

and elsewhere in the application as originally filed.

No new matter is added by way of the amendments to the specification.

The Second Declaration by Dr. Joseph K. Belanoff

Applicant submits herewith a Second Declaration under 37 C.F.R. § 1.132 by Dr. Belanoff. This Second Declaration is submitted to provide further remarks which are believed to make clearer the subject matter discussed by Dr. Belanoff in his previous Declaration under 37 C.F.R. § 1.132 (submitted on December 15, 2017).

In particular, Dr. Belanoff comments on points 8 and 9 of his December 15, 2017 Declaration, and reiterates that the data “was obtained from administering 300 mg per day or 600 mg per day of mifepristone to subjects who also received ketoconazole”, that this data “indicated that this co-administration would be safe,” and that the data “imply that 900 mg and 1200 mg of mifepristone with ketoconazole would also be safely tolerated.”

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joe Belanoff et al.

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION
OF GLUCOCORTICOID RECEPTOR
MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: Chris E. SIMMONS

Technology Center/Art Unit: 1629

SECOND DECLARATION OF JOSEPH K.
BELANOFF UNDER 37 C.F.R. § 1.132

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

Commissioner:

I, Dr. Joseph K. Belanoff, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. My *curriculum vitae* was filed as an Appendix to my previous Declaration submitted on December 15, 2017 regarding U.S. Application 15/627,539.
2. I am the inventor of the subject application.
3. I note that the experiments reported in the subject application entailed administering either 300 mg per day mifepristone or 600 mg per day mifepristone to subjects who also received ketoconazole. The plasma levels of mifepristone and some of its metabolites were measured at various times during the experiments, and are reported in the application.
4. In my Declaration of December 15, 2017 (for example, at point 9), I noted that our data indicated that doses of mifepristone, some in excess of 600 mg, could be safely administered along with a CYP3A inhibitor such as ketoconazole. I reiterate here that the data was obtained from administering 300 mg per day or 600 mg per day of mifepristone to subjects who also received

ketoconazole; and that the data from administration of 300 mg per day or 600 mg per day of mifepristone to subjects who also received ketoconazole indicated that this co-administration would be safe. The data derived from testing 300 mg mifepristone and 600 mg mifepristone with ketoconazole imply that 900 mg and 1200 mg of mifepristone with ketoconazole would also be safely tolerated.

5. In my Declaration of December 15, 2017, I stated (at point 8): "By reducing the mifepristone dose by 33% when administering a CYP3A inhibitor such as ketoconazole, the mifepristone concentration remained within safe, and effective, levels."

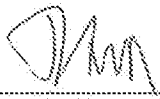
6. I wish to make clear that the statement quoted in point 5 above was not meant to imply that different (e.g., reduced) doses of mifepristone were administered to the same individuals. It was meant to point out that our experimental data indicated that the mifepristone concentration would remain within safe, and effective, levels if the dose of mifepristone were reduced by 33% when it was administered with a CYP3A inhibitor such as ketoconazole.

7. In my Declaration of December 15, 2017, I stated (at point 8): "It was further surprisingly found that in some cases, the mifepristone dose could be titrated upwardly, after the initial reduction, to provide effective treatment while mifepristone levels remained within safe bounds."

8. I wish to make clear that the statement quoted in point 7 above was not meant to imply that different (e.g., upwardly titrated) doses of mifepristone were administered to the same individuals, but was meant to point out that our clinical data indicates that, in some cases, the mifepristone dose may be titrated upwardly, after an initial reduction, to provide safe co-administration of mifepristone and ketoconazole.

9. This Declarant has nothing further to say.

Dated: 1/22/18



Joseph K. Belanoff, M.D.

Electronic Acknowledgement Receipt

EFS ID:	31570655
Application Number:	15627359
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Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	SUPPLEMENTAL_Concomitant_600mg__NF_Resp_due_1_20_18.pdf	167214 b96e7caeee9d6fb86bc1df94c5ff045fd1e2a7e8	no	4

Warnings:

Information:					
2	Affidavit-traversing rejections or objections rule 132	Second_Belanoff_Declaration_15627359.pdf	643304	no	2
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Warnings:					
Information:					
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15/627,359	
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	First Named Inventor		Joseph K. Belanoff	
	Art Unit		1629	
	Examiner Name		Chris E. Simmons	
	Attorney Docket Number		085178-1053027-011410US	

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	E1.	9216221	B2	Dec 22, 2015	Newell-Price	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	E2.	20100135956	A1	Jun 3, 2010	Gant et al.	
	E3.	20160067264	A1	Mar 10, 2016	Newell-Price	

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	E4.	2010052445	WO	A1	May 14, 2010	University of Sheffield		
	E5.	2016187347	WO	A1	Nov 24, 2016	Corcept Therapeutics, Inc.		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	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 ⁵
	E6.	MORGAN et al., "Mifepristone for Management of Cushing's Syndrome", Pharmacotherapy, February 21, 2013, 33(3):319-329	
	E7	VARIS et al., "The Effect of Itraconazole on the Pharmacokinetics and Pharmacodynamics of Oral Prednisolone", European Journal of Clinical Pharmacology, April 2000, 56(1):57-60	
	E8.	PCT/US2018/020336 , "International Search Report and Written Opinion", May 15, 2018, 11 pages	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15/627,359
	Filing Date		June 19, 2017
	First Named Inventor	Joseph K. Belanoff	
	Art Unit	1629	
	Examiner Name	Chris E. Simmons	
	Attorney Docket Number	085178-1053027-011410US	

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			
<p>¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.</p>			

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(74) Agent: **HARRISON IP LIMITED**; Marlborough House, Westminster Place, York Business Park, Nether Poppleton, York YO26 6RW (GB).

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(54) Title: MEDICAMENT AND METHOD OF DIAGNOSIS

(57) Abstract: We disclose a diagnostic test to determine suitable therapeutic intervention of subjects suffering from subclinical Cushing's syndrome [SCS] and also agents that antagonise the action of Cortisol or inhibit excess Cortisol production in the treatment of conditions such as SCS in the presence of an adrenal incidentaloma.

Medicament and Method of Diagnosis

The invention relates to agents that inhibit the production of excess cortisol, or antagonize its effects, in the prevention or treatment of conditions such as subclinical
5 Cushing's syndrome [SCS]; medicaments and pharmaceutical compositions comprising the agents, combinations of agents; and also to a diagnostic test to determine suitable therapeutic intervention of subjects suffering from SCS.

Cortisol, also called the "stress hormone", is secreted by the adrenal glands which are
10 adjacent the kidneys. Cortisol secretion increases when the body is stressed, either physically or psychologically. Cortisol is released from the adrenal gland under the regulation of ACTH derived from the pituitary gland. There is a circadian rhythm to cortisol release with high levels first thing in the morning and very low levels around midnight. ACTH and thus cortisol levels begin to rise between 2 - 3am and peak
15 between 7 - 9 am gradually falling over the day to a nadir between 8pm and 2am. Disease conditions associated with excess cortisol secretion include Cushing's syndrome also referred to as hypercortisolism or hyperadrenocorticism and typically results from excess cortisol production due to a pituitary adenoma. Cushing's syndrome has a complex pathology and symptoms include weight gain, telangiectasia, skin
20 thinning, bruising, insomnia, psychiatric disorders or depression, impaired cognition or memory, osteopenia or osteoporosis, obesity, persistent hypertension, insulin resistance which can lead to impaired fasting glucose or impaired glucose tolerance or diabetes mellitus, dyslipidemia, metabolic syndrome, coagulation disorders, proximal muscle weakness, hirsutism, amenorrhea. Untreated Cushing's disease can result in
25 atherosclerosis, heart disease and increased mortality.

A related disease associated with excess cortisol production is subclinical Cushing's syndrome [SCS]. This condition is commonly associated with adrenal incidentaloma. Incidentaloma's are mostly benign non-secreting tumours discovered by imaging studies
30 performed for unrelated reasons. In approximately 10 to 15% of cases, they produce supraphysiological amounts of cortisol. The levels are insufficient to cause clinical features typically associated with Cushing's syndrome. SCS is common in the general population (~1% or more of those >70y in hospitalized or health-screened populations), and contributes to overall cardiovascular morbidity and mortality. A major problem is
35 that management of SCS is not established. Approximately 90% of patients with SCS have hypertension; over 60% have impaired glucose tolerance or diabetes mellitus,

obesity and osteoporosis or abnormal biochemical markers of bone turnover, 50% have dyslipidemia and abnormalities in hemostatic parameters. Carotid intima-media thickness is increased and atherosclerotic plaques are more frequent in patients than in controls.

5

In SCS there is the potential to permanently reduce these risks, and to improve bone health, by adrenalectomy. Only a very limited number of individuals with SCS are subjected to adrenalectomy. In those that have undergone this procedure improvements have been found in blood pressure (~10mmHg drop in systolic BP), lipid profiles, 10 fibrinogen levels, biochemical markers of bone turnover and glycaemic control. However, a problem is deciding whether adrenal surgery will be of benefit for a given patient with SCS, and the basis for selection for such permanent and invasive intervention is not established.

15 There is a need to provide a treatment regime for controlling SCS and a diagnostic test to determine an appropriate treatment regime for a subject suffering from SCS. The response of subjects to the administration of these agents will also allow an objective means to determine if a subject suffering from SCS would benefit from adrenalectomy.

20 Glucocorticoid receptor antagonists are known in the art. For example mifepristone (11-[4-(Dimethylamino)phenyl]-17-hydroxy-17-[1-propynyl]-[11 β ,17 β]-estra-4,9-dien-3-one), a derivative of the synthetic progestin norethindrone, is a potent competitive glucocorticoid and progesterone receptor antagonist. Mifepristone is also known as RU486. Mifepristone causes glucocorticoid antagonism by reducing translocation of the 25 receptor to the nucleus and also by antagonising glucocorticoid-dependent transcriptional activity. In man the administration of mifepristone at >200mg/day blocks central and peripheral glucocorticoid action with resultant activation of the HPA axis. Selective, nonsteroidal glucocorticoid receptor antagonists have been derived from RU486 for instance as described by Morgan et al. (2002) in J. Med. Chem. 45, 2417- 30 2424, as CP-394531, and CP-409069. A further example is RU43044 which is a selective glucocorticoid receptor antagonist. Other nonsteroidal glucocorticoid receptor antagonist compounds are described for example in following patents and patent applications: US6,380,223, US6,436,986, US6,468,975, US2002/0147336, US 2002/0107235, US2004/0014741, US2004/0176595, WO2004/009017, WO 35 2004/110385, WO2004/111015, US2004/0266758, US2004/0266831, WO2001/16128 WO2006/084917 and WO2008/017658 each of which is incorporated by reference.

An alternative means to oppose the actions of cortisol is to reduce circulating levels by blocking cortisol synthesis using inhibitors of adrenal steroidogenesis. Cortisol synthesis inhibitory properties have been ascribed to several drugs. For instance, ketoconazole, was initially developed as an anti-fungal therapy. The drug inhibits unselectively the synthesis corticosteroids and at higher doses the synthesis of testosterone. Recently, the use of ketoconazole in cardiovascular and metabolic diseases has been claimed by e.g. US 6,274,582, US 6,642,236. Further examples include aminogluthetimide and metyrapone. Aminogluthetimide blocks the conversion of cholesterol to pregnenolone by inhibiting desmolase which inhibits the synthesis of many steroids including cortisol. Metyrapone blocks cortisol synthesis by inhibition of steroid 11 beta hydroxylase. Other examples include trilostane, etomidate, epostane, thiopentone and ketotrilostane.

This disclosure relates to a diagnostic test to determine a suitable treatment regime for a subject suffering from excess cortisol production, for example subclinical Cushing's syndrome and also the treatment of the condition by administration of agents that inhibit the synthesis or activity of cortisol, or by surgical intervention.

STATEMENTS OF INVENTION

According to an aspect of the invention there is provided a diagnostic test, to determine a suitable treatment regime for a subject suffering from or having a pre-disposition to subclinical Cushing's syndrome or incidentaloma comprising:

- i) obtaining a biological sample from the subject; determining the level of cortisol in the subject and comparing this to control cortisol levels as a measure of subclinical Cushing's syndrome;
- ii) administering an effective amount of at least one agent to the subject to inhibit the synthesis or activity of cortisol in the subject; and
- iii) analysing the response of the subject to the administration of the agent to determine the improvement or not of the subject's condition.

In a preferred method of the invention, the diagnostic test aims at developing a clinical decision-making tool to inform the critical decision as to whether to proceed to adrenalectomy or not, or to use glucocorticoid receptor antagonists and/or inhibitor of adrenal steroidogenesis.

In a preferred method of the invention, the diagnostic test aims at developing a clinical decision-making tool to inform if hypertension and/or, glucose metabolism impairment, glucose tolerance impairment, diabetes and/or osteoporosis are cortisol-dependent.

5 In a preferred method of the invention wherein there is an improvement in the subject's condition, the subject is either administered a unit dose of the agent in a controlled regime to maintain control of the subject's condition or to an alternative treatment regime; preferably said alternative treatment regime is surgical intervention, for example adrenalectomy.

10

In an alternative preferred method of the invention wherein the subject's condition does not improve a treatment regime is elected; preferably said alternative treatment regime is to avoid unnecessary surgical intervention, for example adrenalectomy; preferably said alternative treatment regime is to continue symptomatic treatment for hypertension and/or glucose metabolism impairment and/or osteoporosis.

15

In a preferred method of the invention wherein there is an improvement in the subject's condition, this means that the diagnosis test is positive; preferably this means that hypertension and/or glucose metabolism impairment and/or osteoporosis are linked to subclinical Cushing's syndrome or incidentaloma; preferably this means that hypertension and/or glucose tolerance impairment or diabetes and/or osteoporosis are linked to subclinical Cushing's syndrome or adrenal incidentaloma.

20

In an alternative preferred method of the invention wherein the subject's condition does not improve, this means that the diagnosis test is negative; preferably said this means that hypertension and/or glucose metabolism impairment and/or osteoporosis are not linked to subclinical Cushing's syndrome or adrenal incidentaloma; preferably said, this means that hypertension and/or glucose tolerance impairment or diabetes and/or osteoporosis are not linked to subclinical Cushing's syndrome or adrenal incidentaloma.

25
30

In a preferred method of the invention said agent is a glucocorticoid receptor antagonist.

35

The term "glucocorticoid receptor antagonist" refers to any agent which partially or completely inhibits (i.e. antagonizes) the binding of a glucocorticoid receptor agonist, such as cortisol.

In a preferred method of the invention said glucocorticoid receptor antagonist is mifepristone.

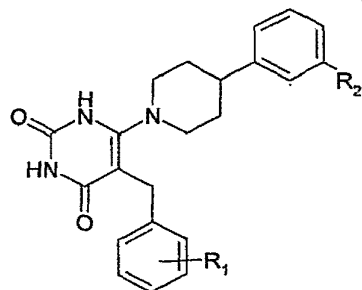
The term "mifepristone" also referred to as RU486 or 17-beta-hydroxy- 11 -beta-(4-dimethyl-aminophenyl)- 17-alpha- (1-propynyl)-estra-4, 9-dien-3 -one, refers to a molecule which belongs to a family of molecules sharing the same mechanism of action), including 11 -beta-(4dimethylaminophenyl)- 17-beta-hydrox17-alpha-(l-propynyl)-estrn-4,9-dien-3-one), or analogues thereof, which bind to the glucocorticoid receptor, typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of cortisol to a glucocorticoid receptor.

In an alternative preferred method of the invention said glucocorticoid receptor antagonist is selected from the group illustrated in Figure 1.

In a most preferred embodiment, the steroidal glucocorticoid receptor antagonist is mifepristone.

Examples of non-steroidal glucocorticoid receptor antagonists include, without limitation, N-(2-[4,4',441 -trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4"-trichlorotrityl]imidazole; 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4"-trichlorotrityl)-1,2,4-triazole-3-thiol;, 4.alpha.(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP 394531") , 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-1 pyrrolidiny]cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine and naloxone.

In another embodiment, the non-steroidal glucocorticoid antagonist is one of the series synthesized by Corcept therapeutics. WO2006/014394, incorporated herein by reference, reports the synthesis and biological characterization of 48 novel 5,6-substituted pyrimidine-2,4-dione GR modulators. The most active compounds are compounds of formula I



(I)

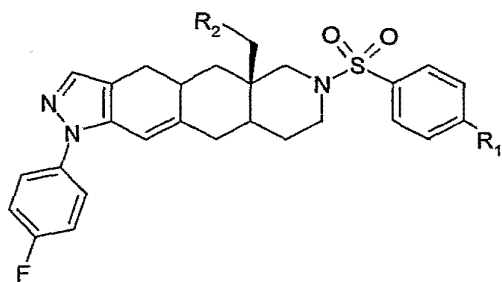
wherein

R1 is H and R2 is H or Cl,

or R1 is o-chloro or m-chloro and R2 is H.

- 5 In WO05/087769, incorporated herein by reference, Corcept therapeutics described the synthesis and biological testing of 150 compounds with a tetracyclic core ring structure that they term as azadecalins. Preferred azadecalin antagonists are compounds of formula II

(II)



10

wherein

R1 is F and R2 is pyrrolidine,

or R1 is t-butyl and R2 is selected from the group consisting of H, a phenyl group, and -CH₂-O-CH₃

15

In a further alternative method of the invention said agent is an inhibitor of adrenal steroidogenesis.

- 20 In a preferred method of the invention said inhibitor of adrenal steroidogenesis is selected from the group consisting of: ketoconazole, metyrapone, aminoglutethimide, trilostane, etomidate, epostane, thiopentone and ketotrilistane.

In a preferred method of the invention said inhibitor of adrenal steroidogenesis is ketoconazole.

In a preferred method of the invention said inhibitor of adrenal steroidogenesis is metyrapone.

- 5 In a preferred method of the invention said agent is a combination of cortisol lowering agents; preferably a combination of a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.

10 According to an aspect of the invention there is provided an agent that inhibits the synthesis or activity of cortisol for use in the prevention or treatment of subclinical Cushing's syndrome.

In a preferred embodiment of the invention subclinical Cushing's syndrome is caused by an adrenal incidentaloma.

15

According to an aspect of the invention there is provided an agent that inhibits the synthesis or activity of cortisol for use in the prevention or treatment of incidentaloma.

In a preferred embodiment of the invention agent is a glucocorticoid receptor antagonist.

20

In a preferred embodiment of the invention said glucocorticoid receptor antagonist is mifepristone.

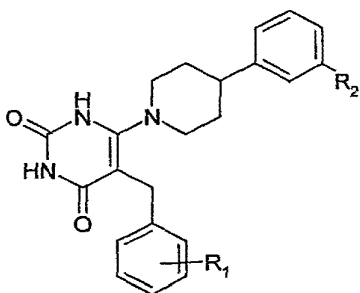
25 In an alternative preferred embodiment of the invention said glucocorticoid receptor antagonist is RU-43044, Org 34517, Org 34850, or Org 34116.

In a most preferred embodiment, the steroidal glucocorticoid receptor antagonist is mifepristone.

30 Examples of non-steroidal glucocorticoid receptor antagonists include, without limitation, N-(2-[4,4',4''-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4''-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4'']-trichlorotrityl)imidazole; 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4''-trichlorotrityl)-1,2,4-triazole-3-thiol; 4.alpha.(S)-Benzyl-2(R)-
35

chloroethyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP 394531") , 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-1 pyrrolidinyl]cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine and
 5 naloxone.

In another embodiment, the non-steroidal glucocorticoid antagonist is one of the series synthesized by Corcept therapeutics. WO2006/014394, incorporated herein by reference, reports the synthesis and biological characterization of 48 novel 5,6-
 10 substituted pyrimidine-2,4-dione GR modulators. The most active compounds are compounds of formula I



(I)

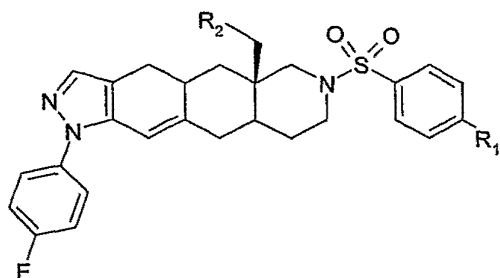
wherein

R₁ is H and R₂ is H or Cl,

15 or R₁ is o-chloro or m-chloro and R₂ is H.

In WO05/087769, incorporated herein by reference, Corcept therapeutics described the synthesis and biological testing of 150 compounds with a tetracyclic core ring structure that they term as azadecalins. Preferred azadecalin antagonists are compounds of
 20 formula II

(II)



wherein

R₁ is F and R₂ is pyrrolidine,

or R1 is t-butyl and R2 is selected from the group consisting of H, a phenyl group, and -CH₂-O-CH₃

5 In an alternative embodiment of the invention said agent is an inhibitor of adrenal steroidogenesis.

In a preferred embodiment of the invention said inhibitor of adrenal steroidogenesis is selected from the group consisting of: ketoconazole, metyrapone, aminoglutethimide, trilostane, etomidate, epostane, thiopentone and ketotrilostane.

10

In a preferred embodiment of the invention said agent is a combination of agents that inhibit the synthesis or activity of cortisol; preferably a combination of a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.

15 According to a further aspect of the invention there is provided a pharmaceutical composition comprising: a glucocorticoid receptor antagonist, an inhibitor of adrenal steroidogenesis and an excipient.

20 The compositions of the invention are administered in effective amounts. An "effective amount" is that amount of a composition that alone, or together with further doses, produces the desired response. For example, a dose of 100-300mg mifepristone or more preferably 200mg mifepristone twice daily is administered to provide partial blockade of glucocorticoid receptor activity. Such amounts will depend, of course, on the particular condition being treated, the severity of the condition, the individual patient
25 parameters including age, physical condition, size and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the
30 individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a patient may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

35 In the case of treating SCS the desired response is the symptomatic treatment of the consequences of the disease. This may involve only the partial improvement of the

symptomatic consequences of the disease, although more preferably, it involves complete improvement of the symptomatic consequences of the disease. This can be monitored by routine methods. More particularly improvements in SCS can be monitored by any one of the following indicia:

5

Blood pressure: The difference in blood pressure compared to baseline, in systolic and/or diastolic blood pressure (BP) (resting and ambulatory)

Glucose homeostasis: Homeostasis model assessment of insulin resistance (HOMA-IR), and the insulin Sensitivity Index (ISI) as calculated from oral glucose tolerance test:
10 insulin and glucose at -15, 0, 30, 60 and 120 minutes, with oral glucose 75g at time 0 (except for those on insulin therapy, whose investigation will be limited to basal and 120 minute plasma glucose) and 2-hour glucose tolerance during a 75g oral glucose tolerance test.

15

Lipid profiling: The difference in fasting lipids post treatment.

DEXA scan with measurement of total and abdominal fat mass: The difference in total
20 and abdominal fat mass post treatment compared to baseline.

Bone Markers: Excess cortisol will suppress serum osteocalcin, a marker of bone formation, and thus the effect of antagonism of glucocorticoids or lowering cortisol is an increase in this marker, and give insight as to the effect on bone health. The other bone
25 turnover markers are bone alkaline phosphatase, C-telopeptide I (CTX-I) and N-terminal propeptide of type 1 procollagen (P1NP) are expected to decrease.

Urine steroid profile: The difference in urinary steroid profile post treatment.

30 Quality of Life: The difference between in depression, quality of life and fatigue questionnaires.

The pharmaceutical compositions used in the foregoing methods preferably are suitable for oral administration and contain an effective amount of an agent according to the
35 invention for producing the desired response in a unit of weight or volume suitable for administration to a patient. The response can, for example, be measured by determining decrease of disease symptoms.

The doses of the agent according to the invention administered to a subject can be

chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment, subject's body mass index, ACTH or cortisol (in plasma, urine or salivary) levels. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

Other protocols for the administration of agents will be known to one of ordinary skill in the art, in which the dose amount, schedule and mode of administration and the like vary from the foregoing. The administration of compositions to mammals other than humans, (e.g. for testing purposes or veterinary therapeutic purposes), is carried out under substantially the same conditions as described above. A subject, as used herein, is a mammal, preferably a human, and including a non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent.

When administered, the agents of the invention are applied in pharmaceutically-acceptable amounts and in pharmaceutically-acceptable compositions. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically-acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically-acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts. The compositions also may contain, optionally, suitable preservatives, such as: benzalkonium chloride; chlorobutanol; parabens and thimerosal. The agents of the invention can exist in different forms, such as acids, esters, salts and tautomers, for example, and the invention includes all variant forms of the agents.

Compositions may be combined, if desired, with a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more

compatible solid or liquid fillers, diluents or encapsulating substances which are suitable for administration into a human. The term "carrier" in this context denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application, [e.g. liposome based]. The components of the pharmaceutical compositions also are capable of being co-mingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well-known in the art of pharmacy. All methods include the step of bringing the active agent into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units, such as capsules, tablets, lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquids or non-aqueous liquids such as syrup, elixir or an emulsion or as a gel. Compositions may be administered as aerosols and inhaled.

Compositions suitable for parenteral administration conveniently comprise a sterile aqueous or non-aqueous preparation of agent which is preferably isotonic with the blood of the recipient. This preparation may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation also may be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1, 3-butane diol. Among the acceptable 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 di-glycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables. Carrier formulation suitable for oral, subcutaneous, intravenous, intramuscular, etc. administrations can be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

According to a further aspect of the invention there is provided a method of treating

subclinical Cushing's syndrome comprising administering an effective amount of at least one agent that inhibits the synthesis or activity of cortisol. .

5 According to a further aspect of the invention there is provided a method of treating subclinical Cushing's syndrome comprising administering an effective amount of a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.

10 Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", means "including but not limited to", and is not intended to (and does not) exclude other moieties, additives, components, integers or steps.

15 Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

20 Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

An embodiment of the invention will now be described by example only and with reference to the following figures, materials and methods:

25

Figure 1 illustrates non-limiting examples of glucocorticoid receptor antagonists;

30 Figure 2 illustrates a non-limiting embodiment of the treatment regime herein disclosed; Mifepristone test demonstrates if diabetes or hypertension are caused by sub-clinical Cushing's syndrome or not (are cortisol-dependent or not); and

35 Figure 3 illustrates a further embodiment of the treatment regime herein disclosed. Diagnostic Test for subclinical CS- incidentaloma This test will help to select which patient would benefit from adrenalectomy

Methodology

Determination of Cortisol Excess

5 Three main tests are used to demonstrate excess cortisol secretion: urinary free cortisol, dexamethasone suppression tests, and midnight plasma or salivary cortisol. In SCS urinary free cortisol is usually within the normal range, as this is a relatively insensitive marker of hypercortisolaemia, whilst a post-dexamethasone serum value of >60nM (>1.9ug/dl) in patients with adrenal incidentalomas is associated with excess
10 hypertension, as is an elevated midnight cortisol sample. Plasma ACTH levels are usually in the lower end of the normal range, reflecting low-grade partial hypothalamo-pituitary-adrenal axis suppression, as a consequence of the low-grade excess autonomous secretion of cortisol from the adrenal.

15 In addition to these tests urinary steroid metabolite analysis by gas chromatography/mass spectrometry (GC/MS) is an invaluable tool allowing detailed analysis of the complete steroid output of an individual and, importantly, by analyzing substrate/product ratios, it facilitates the calculation of measures of steroidogenic enzyme activity. Decreased 5-alpha-reductase activity is a specific feature of Cushing's
20 syndrome and distinguishes it from the polycystic ovary syndrome that is associated with increased 5alpha-reductase activity, though clinically both conditions may present with features of the metabolic syndrome (obesity, hypertension, impaired glucose tolerance). In addition urinary steroid GC/MS analysis allows the identification of decreased 11-beta-HSD2 activity in severe overt Cushing's syndrome due to the ectopic ACTH syndrome, a
25 feature that is not apparent in SCS. GC/MS analysis will allow for a more detailed picture on the nature of glucocorticoid excess in adrenal incidentaloma than urinary free cortisol excretion alone.

Design

30 The period of study is 8 weeks. The first 4 intervention visits are weekly, and the next two 2-weekly. The overall study design and assessments is shown in Table 1, including assessments made for secondary endpoints: Intervention - Mifepristone 200mg BD from week 0

Inclusion criteria

35 Patients are eligible for inclusion if: they are over 18; have an adrenal incidentaloma with benign characteristics as assessed on CT or MRI; lack clinical features classically associated with Cushing's syndrome; have evidence of excess cortisol as shown by lack

of suppression of serum cortisol on 1mg over-night dexamethasone suppression or 2mg /day 48 hour low-dose dexamethasone suppression testing; stable antihypertensive and diabetic medication for two months prior to study entry.

5 Exclusion criteria

These include: evidence of local or systemic malignancy; overt Cushing's syndrome; severe uncontrolled diabetes mellitus or hypertension; Clinically significantly impaired cardiovascular function (e.g. stage IV cardiac failure); severe liver disease (liver enzymes ≥ 3 x the institutional upper limit of normal range); significantly impaired renal function (eGFR <30 /min); uncontrolled severe active infection; treatment with approved or experimental steroidogenesis inhibitors, adrenolytic agents, within four weeks of admission; In women, known endometrial cancer, history of endometrial hyperplasia or vaginal bleeding of unknown cause; requirement for inhaled or systemic glucocorticoids for existing disease; impaired mental capacity or markedly abnormal psychiatric evaluation that precludes informed consent.

Treatment regime

20 The dose of 200mg twice daily is administered to provide blockade of glucocorticoid receptor activity. The interval is twice daily based on the known half-life of the drug and the wish to *completely block* glucocorticoid activity over the 24-hour period, with reduced risk of overt glucocorticoid deficiency, and to minimize the possibility of a rebound effect of increased cortisol exposure at the end of the dose interval, as may happen by using a
25 single dose of mifepristone 400mg/24 hours.

Safety

Clinical assessment by BP, P, temperature, weight and questioning for fatigue, headache, anorexia, nausea, arthralgia, myalgia, and abdominal pain (potential glucocorticoid deficiency, a predictable effect of mifepristone based on its known action) is made at each study visit. Clinical experience is, however, that even total adrenal insufficiency is well tolerated in the absence of physical or infective stressors. For safety purposes each patient is issued with a steroid card and with a supply of two
35 dexamethasone 1mg tablets (sufficient to overcome the effects of mifepristone 400mg by taking dexamethasone 1mg/day for 2 days) to be taken on the advice of the

investigators if significant symptoms are reported. In such circumstances any study subject attends the Clinical Research Facility (CRF) either that day or the next working day, and data entered into the CRF accordingly, and the subject withdrawn. Other uncommon but documented side effects of mifepristone used at this dose and for this
5 time period include: nausea, anorexia, asthenia, skin rash (maculopapular), increased eosinophil count, joint pain, hypokalaemia. When used for >3-6 months duration endometrial hyperplasia, vaginal bleeding, metrorrhagia and amenorrhea are described, ..

Statistical Analysis

10

This protocol follows an open-label, non-randomised design. All statistical analyses are performed with descriptive and exploratory purposes and the results of statistical tests with confidence interval, when given is considered an aid to evaluate the reliability of the observed result. The data is summarised with respect to demographic and baseline
15 characteristics, efficacy, observation and measurements, safety observations and measurements.

The primary outcome analysed is change in the resting and 24-hour ambulatory blood pressure, and the 2-hour glucose on OGTT. Secondary endpoints are analysed in a
20 similar fashion.

Outcome measures

Primary end points are the difference at 8 weeks, compared to baseline, in systolic
25 blood pressure (BP) (resting and ambulatory) and 2-hour glucose tolerance during a 75g oral glucose tolerance test. BP is measured in the sitting position, left arm taken twice, separated by 5 mins, after 10 mins resting (according to British Hypertension Society, UK [BHS] guidelines). 24-hour ambulatory blood pressure will be measured using standard BHS-approved monitors.

30

The primary endpoints have been chosen, as they are associated with important clinical outcomes. Baseline 24 hour ambulatory BP monitoring will be performed between the first visit and randomisation (4 week interval) and again at weeks 4 and 8. The daytime and nocturnal BP as determined by 24-hour ambulatory monitoring will be assessed
35 independently and together to take account of the influence of the circadian rhythm in serum cortisol

- Secondary end points** are: compared to baseline: 1) the difference in BP and Glucose tolerance at 4 weeks; 2) homeostasis model assessment of insulin resistance (HOMA-IR), and the insulin Sensitivity Index (ISI) at 4 and 8 weeks, as calculated from oral glucose tolerance test: insulin and glucose at -15, 0, 30, 60 and 120 minutes, with oral glucose 75g at time 0 (except for those on insulin therapy, whose investigation will be limited to basal and 120 minute plasma glucose); 3) the difference in the mean plasma 0900h plasma ACTH, and salivary 0900 and 2400h cortisol values at 4 and 8 weeks; 4) the difference in fasting lipids at 8 weeks; 5) the difference in bone turnover markers at 8 weeks; 6) difference in urinary steroid profile at week 8; 7) the difference between in depression, quality of life and fatigue questionnaires at 4 and 8 weeks. Tertiary endpoint will be any major cardiovascular adverse events at 8 weeks. Other biochemical safety parameters are summarized in the table above.
- 15 The level of morning plasma ACTH and salivary nocturnal cortisol increases under the action of the study drug and give a biological marker for the effect of blockade. The repeated measurement will give greater confidence in the observation of drug activity. Salivary cortisol is stable at room temperature and thus is collected by patients at home and brought or sent to the CRF. Similarly, assessment of the urinary steroid profile is
- 20 determined to assess the effects of mifepristone and the influence of increased circulating ACTH. Excess cortisol will suppress serum osteocalcin, a marker of bone formation, and thus the predicted effect of mifepristone would be an increase in this marker, and give insight as to the effect on bone health.
- 25 Clinically overt Cushing's syndrome is associated with impairments in health-related subjective health status that does not fully return to normal for many years after treatment. In SCS it is not established if quality of life is impaired. In view of this and the potential effects of altering excess cortisol on mood and general well-being, three validated questionnaires are used to assess the effects of mifepristone therapy on
- 30 health-related subjective health status. In addition to assessing any changes induced by mifepristone therapy the scores are compared to sex and age-matched controls drawn from questionnaire-specific reference cohorts (available at the University of Sheffield), to establish if these parameters are impaired in SCS.

Intervention

Treatment is in the form of an oral tablet of oral mifepristone twice-daily 200mg (0900h and 2100h) for eight weeks. Patients attend the CRF at 0900h fasted at weekly intervals
5 from weeks 0-4, and then again at weeks 6 and 8. A major advantage to this study design, compared to performing adrenalectomy, is that the treatment is immediately reversible, is not associated with the inherent risks of surgery, and it will inform design of a larger study, and then whether an invasive approach by adrenal surgery is justified for study in this common patient group.

10

Instruments

A). *Depression* is measured by Beck Depression Inventory © (BDI®-II). The BDI-II takes approximately 10 minutes to complete. Each item has one numerical answer ranging
15 from 0 (low depression) to 3 (maximum depression). Thus the total score ranges from 0 to 63.

B). *Quality of life* is measured by the Short Form (SF-36), a 36-item health survey questionnaire to record general well-being during the previous 30 days and overall
20 evaluation of health. Scores are expressed on a 0-100 scale, and higher scores are associated with a better quality of life.

C). *Fatigue* is measured by Multidimensional Fatigue Index (MFI-20). This is a 5-point scale that comprises 20 statements to assess fatigue. Scores vary from 0-20, a high
25 score indicating higher experienced fatigue.

30

35

40

Table 1

Week	-	0	1	2	3	4	6	8
Visit	1	2	3	4	5	6	7	8
Informed Consent	✓							
Resting BP and clinical assessment	✓	✓	✓	✓	✓	✓	✓	✓
24-hour BP (during week of study)	✓					✓		✓
OGTT - 0,15,30,60,90,120 mins samples for insulin and glucose		✓				✓		✓
U+E	✓	✓	✓	✓	✓	✓	✓	✓
LFT	✓							✓
TSH	✓							✓
FBC	✓	✓				✓		✓
Fasting lipids		✓						✓
0900h/2400h salivary cortisol	✓	✓	✓	✓	✓	✓	✓	✓
0900h serum cortisol		✓	✓	✓	✓	✓	✓	✓
Plasma ACTH		✓	✓	✓	✓	✓	✓	✓
Bone turnover markers – formation, serum osteocalcin; resorption, urine NTX		✓						✓
Urinary steroid profile (during week of study)	✓							✓
Health-related quality of life questionnaires	✓					✓		✓

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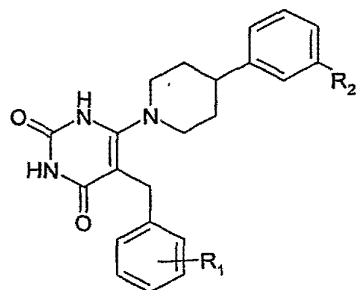
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Claims

- 1 An agent that inhibits the synthesis or activity of cortisol for use in the prevention
5 or treatment of subclinical Cushing's syndrome.
- 2 An agent that inhibits synthesis or activity of cortisol for use in the prevention or
treatment of incidentaloma.
- 10 3. The agent according to claim 1 wherein subclinical Cushing's syndrome is
caused by an adrenal incidentaloma.
4. The agent according to any of claims 1 to 3 wherein said agent is a
glucocorticoid receptor antagonist.
- 15 5. The agent according to claim 4 wherein said glucocorticoid receptor antagonist is
selected from the group as illustrated in Figure 1.
6. The agent according to claim 5 wherein said glucocorticoid receptor antagonist is
20 mifepristone.
7. The agent according to claim 4 wherein said antagonist is a non-steroidal
glucocorticoid receptor antagonist.
- 25 8. The agent according to claim 7 wherein said non-steroidal glucocorticoid receptor
antagonist is selected from the group consisting of, N-(2-[4,4',441 -
trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4-(2
hydroxyethyl)piperazine dimaleate; N-([4,4',4"-trichlorotrityl)imidazole; 9-(3-mercapto-
1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-
30 (morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-
phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-
triazole; 1,S-bis(4,4', 4"-trichlorotrityl)-1,2,4-triazole-3-thiol,; 4.alpha.(S)-Benzyl-2(R)-
chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP
394531") , 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-
35 octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-
[2-1 pyrrolidiny]cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine and
naloxone.

9. The agent according to claim 7 wherein said non-steroidal glucocorticoid antagonist is represented by formula I:



(I)

5 wherein

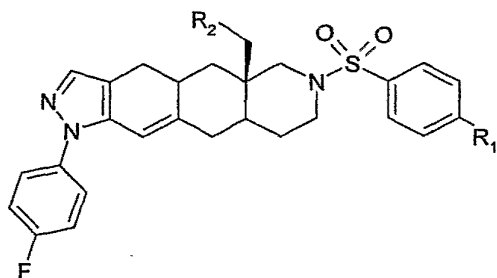
R1 is H and R2 is H or Cl,

or R1 is o-chloro or m-chloro and R2 is H.

10. The agent according to claim 4 wherein said glucocorticoid receptor antagonist is an azadecalin.

11. The agent according to claim 10 wherein said azadecalin is represented by formula II:

15 (II)



wherein

R1 is F and R2 is pyrrolidine,

or R1 is t-butyl and R2 is selected from the group consisting of H, a phenyl group, and -

20 CH₂-O-CH₃

12. The agent according to any of claims 1 to 3 wherein said agent is an inhibitor of adrenal steroidogenesis.

13. The agent according to claim 12 wherein said inhibitor of adrenal steroidogenesis is selected from the group consisting of: ketoconazole, metyrapone, aminoglutethimide, trilostane, etomidate, epostane, thiopentone and ketotrilostane.
- 5 14. The agent according to claim 13 wherein said inhibitor of adrenal steroidogenesis is ketoconazole.
15. The agent according to claim 13 wherein said inhibitor of adrenal steroidogenesis is metyrapone.
- 10 16. The agent according to any of claims 1 to 3 wherein said agent is a combination of agents that inhibit the synthesis or activity of cortisol.
- 15 17. The agent according to claim 16 wherein said combination of agents is a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.
18. A pharmaceutical composition comprising: a glucocorticoid receptor antagonist, an inhibitor of adrenal steroidogenesis and a pharmaceutical excipient.
- 20 19. A method of treating subclinical Cushing's syndrome comprising administering an effective amount of an agent that inhibits the synthesis or activity of cortisol.
20. A method of treating incidentaloma comprising administering an effective amount of an agent that inhibits the synthesis or activity of cortisol.
- 25 21. A method of treating subclinical Cushing's syndrome comprising administering an effective amount of a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.
- 30 22. A method of treating incidentaloma comprising administering an effective amount of a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.
- 35 23. A method to determine a suitable treatment regime for a subject suffering from or having a pre-disposition to subclinical Cushing's syndrome or incidentaloma, said method comprising:

- 5
- i) determining the level of cortisol in a sample from the subject and comparing said level to control cortisol levels as a measure of subclinical Cushing's syndrome;
 - ii) administering to the subject an effective amount of at least one agent that inhibits the synthesis or activity of cortisol; and
 - iii) analysing the improvement of hypertension and/or glucose metabolism and/or osteoporosis in said subject as a measure of the response of the subject to the administration of the agent, to determine an improvement or not of the subject's condition and define a suitable treatment regime..
- 10

24. The method according to claim 23 wherein an improvement in the subject's condition indicates the subject can be treated by surgical intervention

15 25. The method according to claim 23 wherein, if the subject's condition does not improve, the subject shall be submitted to an alternative treatment regime comprising symptomatic treatment for hypertension and/or glucose metabolism impairment and/or osteoporosis.

20 26. The method according to claim 24 wherein said surgical intervention is adrenalectomy.

27. The method according to claim 23 or 24 wherein said agent is a glucocorticoid receptor antagonist.

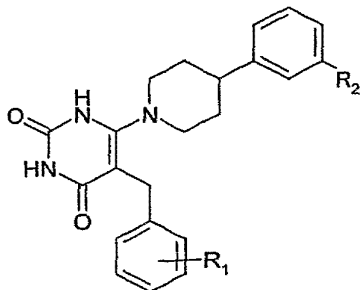
25 28. The method according to claim 27 wherein said glucocorticoid receptor antagonist is selected from the group as illustrated in Figure 1.

29. The method according to claim 27 wherein said glucocorticoid receptor antagonist is mifepristone.

30 30. The method according to claim 23 or 24 wherein said agent is a non-steroidal glucocorticoid receptor antagonists.

31. The method according to claim 30 wherein said non-steroidal glucocorticoid receptor antagonists is selected from the group consisting of: N-(2-[4,4',4''-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4''-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4''-trichlorotrityl])imidazole; 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4', 4''-trichlorotrityl)-1,2,4-triazole-3-thiol; 4.alpha.(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP 394531") , 4.alpha. (S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4.alpha.,9,10,10.alpha. (R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-1 pyrrolidinyl]cyclohexyl]benzeneacetamide, bremazocine, ethylketocyclazocine and naloxone.

32. The method according to claim 30 wherein said non-steroidal glucocorticoid antagonist is represented by formula I:



(I)

wherein

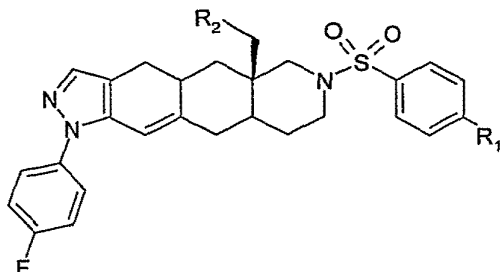
R1 is H and R2 is H or Cl,

or R1 is *o*-chloro or *m*-chloro and R2 is H.

33. The method according to claim 23 or 24 wherein said glucocorticoid receptor antagonist is an azadecalin.

34. The method according to claim 33 wherein said azadecalin antagonist is represented by formula II:

(II)



5 wherein

R1 is F and R2 is pyrrolidine,

or R1 is t-butyl and R2 is selected from the group consisting of H, a phenyl group, and -CH₂-O-CH₃

10 35. The method according to claim 23 or 24 wherein said agent is an inhibitor of adrenal steroidogenesis.

36. The method according to claim 35 wherein said inhibitor of adrenal steroidogenesis is selected from the group consisting of: ketoconazole, metyrapone,
15 aminoglutethimide, trilostane, etomidate, epostane, thiopentone and ketotrilostane.

37. The method according to claim 36 wherein said inhibitor of adrenal steroidogenesis is ketoconazole.

20 38. The method according to claim 36 wherein said inhibitor of adrenal steroidogenesis is metyrapone.

39. The method according to claim 23 wherein said agent is a combination of agents that inhibit the synthesis or activity of cortisol.

25

40. The method according to claim 39 wherein said combination is a glucocorticoid receptor antagonist and an inhibitor of adrenal steroidogenesis.

30

Figure 1

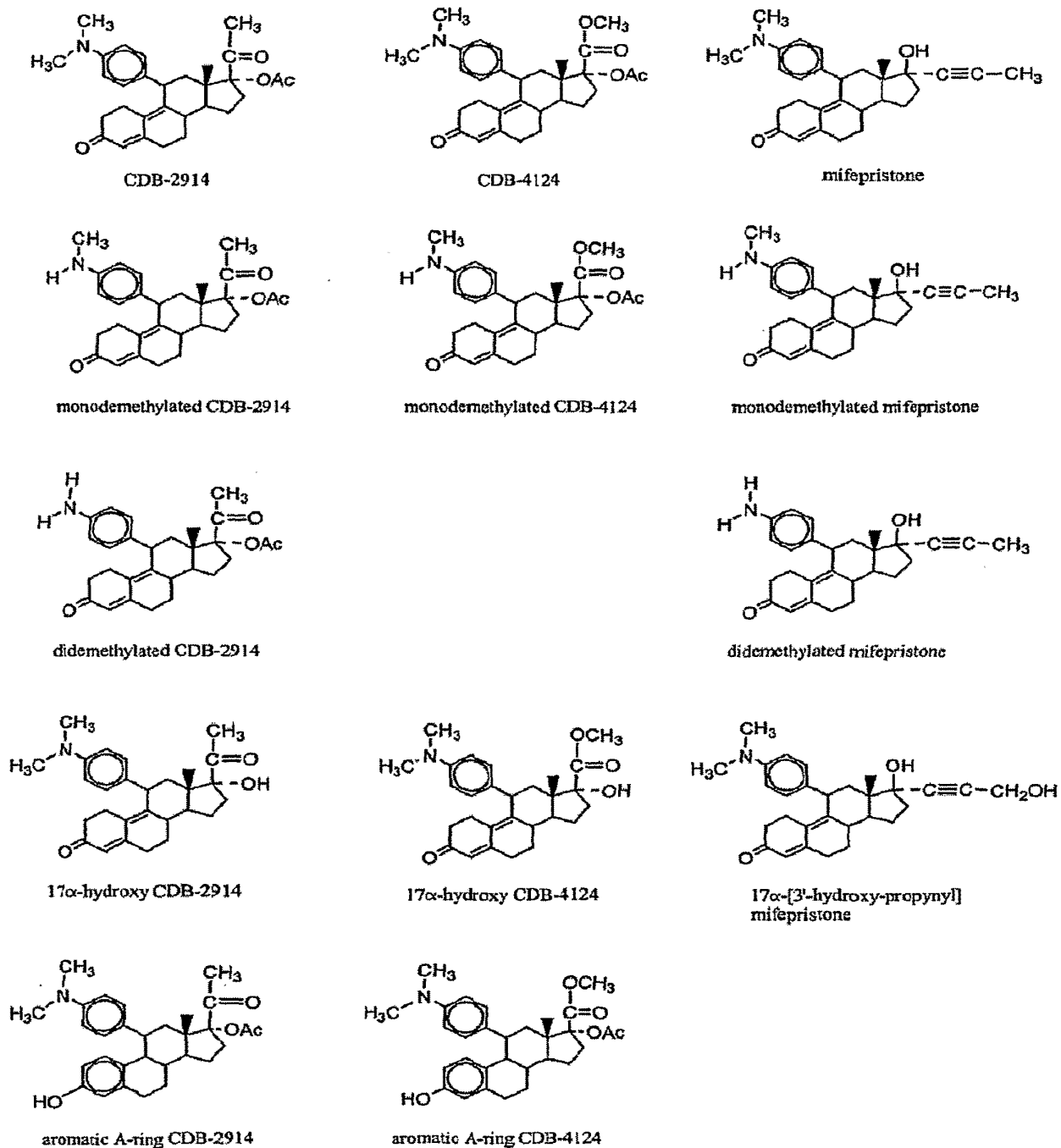


Figure 2

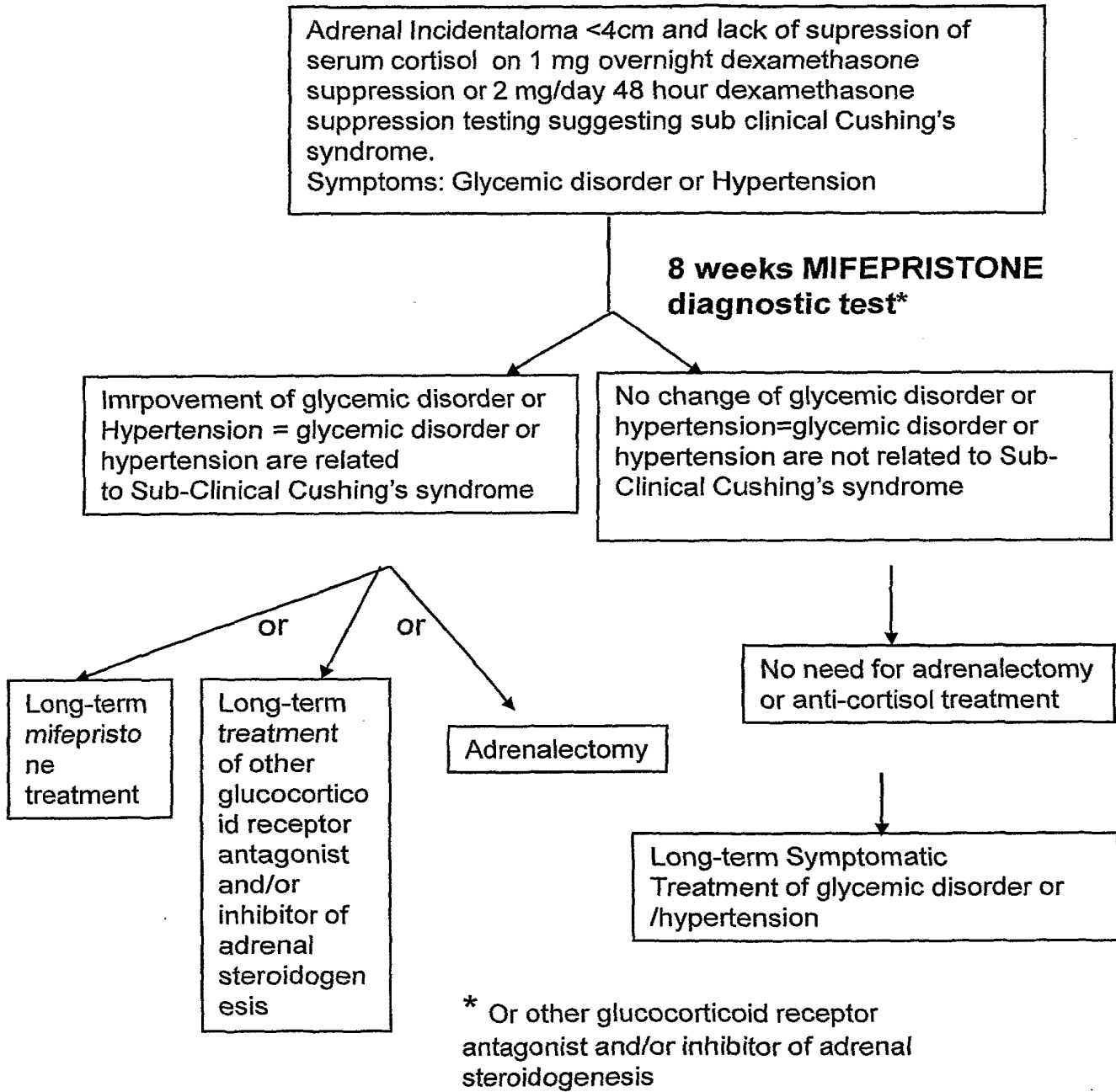
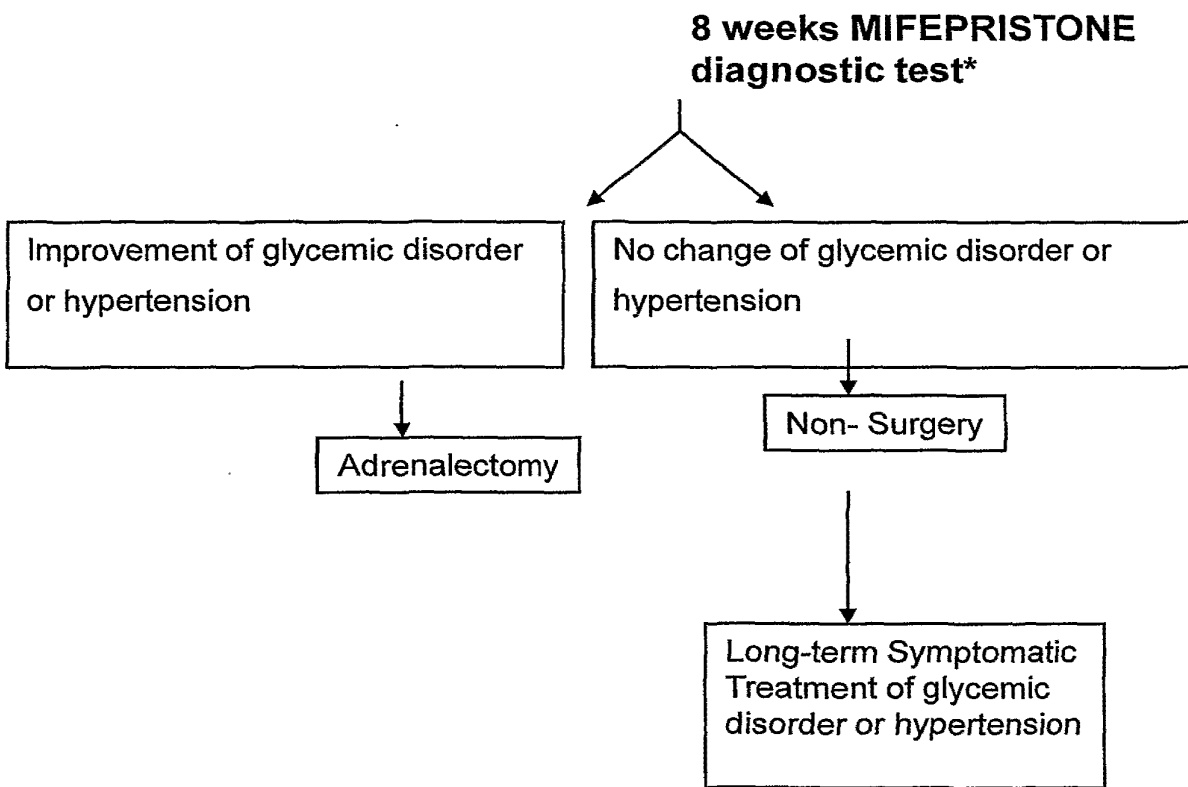


Figure 3

Adrenal Incidentaloma <4cm and lack of suppression of serum cortisol on 1 mg overnight dexamethasone suppression or 2 mg/day 48 hour dexamethasone suppression testing suggesting sub clinical Cushing's syndrome.

Symptoms: Glycemic disorder or Hypertension



* Or other glucocorticoid receptor antagonist and/or inhibitor of adrenal steroidogenesis

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003751

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/10	A61K31/165	A61K31/18	A61K31/357	A61K31/40
A61K31/415	A61K31/4164	A61K31/4196	A61K31/439	A61K31/44
A61K31/485	A61K31/496	A61K31/515	A61K31/5375	A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OHMORL NARIKO ET AL: "Preclinical cushing's disease characterized massive adreanl hyperplasia and hormonal changes after three years of metyrapone therapy" ENDOCRINE JOURNAL, TOKYO, JP, vol. 54, no. 3, 1 June 2007 (2007-06-01), pages 391-397, XP009119938 ISSN: 0918-8959 abstract page 392, left-hand column, line 4 - page 394, left-hand column, line 19 page 395, left-hand column, line 8 - page 396, right-hand column, line 11	1-22
Y	----- -/--	1-40

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

15 July 2009

Date of mailing of the international search report

31/07/2009

Name and mailing address of the ISA/

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Tullberg, Erik

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/003751

C(Continuation): DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOFLE G ET AL: "Adrenocortical carcinoma evolving after diagnosis of preclinical Cushing's syndrome in an adrenal incidentaloma. A case report" HORMONE RESEARCH, S. KARGER AG, BASEL, vol. 50, no. 4, 1 October 1998 (1998-10-01), pages 237-242, XP009120030 ISSN: 0301-0163 abstract	1-22
X	WO 2005/118581 A (SPEEDEL EXPERIMENTA AG [CH]; HEROLD PETER [CH]; MAH ROBERT [CH]; TSCHI) 15 December 2005 (2005-12-15) page 1, lines 1-3 page 8, line 15 - page 9, line 30	1-22
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X	WO 00/54766 A (HORTICULTURE AND FOOD RESEARCH [NZ]; COOK CHRISTIAN JOHN [NZ]) 21 September 2000 (2000-09-21) page 12, lines 15-24 page 14, lines 23-32	18
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A	REZNIK Y ET AL: "Aberrant adrenal sensitivity to multiple ligands in unilateral incidentaloma with subclinical autonomous cortisol hypersecretion: A prospective clinical study" CLINICAL ENDOCRINOLOGY 200409 GB, vol. 61, no. 3, September 2004 (2004-09), pages 311-319, XP002537206 ISSN: 0300-0664 the whole document	

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/003751

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BENAGIANO GIUSEPPE ET AL: "Selective progesterone receptor modulators 3: use in oncology, endocrinology and psychiatry" EXPERT OPINION ON PHARMACOTHERAPY, ASHLEY, LONDON, UK, vol. 9, no. 14, 1 October 2008 (2008-10-01), pages 2487-2496, XP009110411 ISSN: 1465-6566 the whole document	1-40
A	REINCKE M: "Subclinical Cushing's syndrome" ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA, W.B. SAUNDERS COMPANY, PHILADELPHIA, vol. 29, no. 1, 1 March 2000 (2000-03-01), pages 43-56, XP009119921 ISSN: 0889-8529 the whole document	1-40
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A	WO 02/080930 A (WOOD CHRISTOPHER [GB]; MARGETTS GEORGE [GB]) 17 October 2002 (2002-10-17) the whole document	1-40
A	WO 2005/087769 A (CORCEPT THERAPEUTICS INC [US]; CLARK ROBIN D [US]; RAY NICHOLAS C [GB]) 22 September 2005 (2005-09-22) cited in the application the whole document	1-40
A	US 2002/147336 A1 (DOW ROBERT L [US] ET AL) 10 October 2002 (2002-10-10) cited in the application the whole document	1-40
A	US 2004/266831 A1 (ROBINSON LESLIE A [US] ET AL) 30 December 2004 (2004-12-30) cited in the application the whole document	1-40
	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003751

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 2006/014394 A (CORCEPT THERAPEUTICS INC [US]; CLARK ROBIN D [US]; RAY NICHOLAS C [GB]) 9 February 2006 (2006-02-09) cited in the application the whole document</p> <p style="text-align: center;">-----</p>	1-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/003751

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB2008 /003751

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

The present application does not fulfill the requirement of Article 6 PCT for the following reasons:

-the expressions "an agent that inhibits the synthesis or activity of cortisol" according to the subject-matter of claims 1, 2, 16, 20, 23 and 39; "glucocorticoid receptor antagonist" according to the subject-matter of claims 4, 17, 18, 21, 22, 27, 30 and 40 and "inhibitor of adrenal steroidogenesis according to the subject-matter of claims 12, 17, 18, 21, 22, 35 and 40 are not clear because they are open-ended. Therefore, these expressions have been interpreted in light of the subject-matter of claims 5-11, 13-15, 28, 29 and 31-34 and the search has been restricted to these compounds.

-the subject-matter of claim 1-3 is not clear in light of the interpretation conferred by claim 16 which relates to a combination of agents whereas claims 1-3 does not envisage this possibility.

-there appears to be an error in some structures in Figure 1 according to the subject-matter of claims 4 and 28, indeed the compounds CDB-4124 and derivatives thereof are depicted as methyl esters but according to general knowledge they should be methoxymethyl ketones.

-the compounds of formula II according to the subject-matter of claims 11 and 34 are disclosed as tetracyclic azadecalins however the prior art to which it refers invariably discloses tricyclic azadecalin derivatives.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/003751

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/003751

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