



No. 09-055461- -00006-0000

Fecha: 2010-11-17 15:42:25 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 92

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

**SOLICITUD
PUBLICADA**

Numero del expediente: 09 055 461
Solicitante: JANSSEN PHARMACEUTICA N.V.
Apoderado: DILIA MARIA RODRIGUEZ D' ALEMAN
Titulo de la nueva creación o denominación del signo: "METODOS PARA EL TRATAMIENTO DEL ABUSO ADICCION Y DEPENDENCIA DEL ALCOHOL"
Gaceta: 619

③

OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A.
Dirección: CALLE 80 No. 78b-201
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA

Teléfono: 371 99 00 Fax: 373 08 18
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 890.106.527-5

**REPRESENTANTE
O APODERADO**

Nombre: ELIANA ISAURA MORENO BOHORQUEZ
Dirección: CARRERA 13 No. 119-95
Teléfono: (571)213 12 13 Fax: (571)612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 51'975.664 TP.83823

④

FUNDAMENTOS DE LA OPOSICIÓN:

Causa: Art. 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN
No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISaura MORENO BOHORQUEZ

FIRMA:



C.C. 51'975.664

TP. 83823



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 055461

Asunto : Oposición a la solicitud de patente de Invención titulada
“METODOS PARA EL TRATAMIENTO DEL ABUSO,
ADICCION Y DEPENDENCIA DEL ALCOHOL”

Solicitante : JANSSEN PHARMACEUTICA N.V.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 619 del 19 de agosto de 2010

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** Conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada “**METODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCION Y DEPENDENCIA DEL ALCOHOL**”, cuyos titulares son **JANSSEN PHARMACEUTICA N.V.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

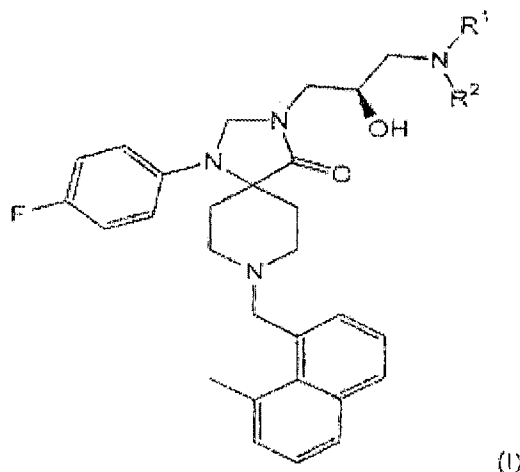
1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular MODULADORES DE ORL-1. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

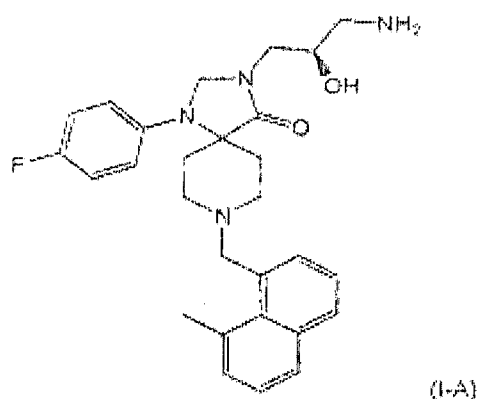
2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 29 de mayo de 2009 reivindicando prioridad bajo la solicitud US20060861375 del 2006-11-28; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 619 del 19 de agosto de 2010, cuya publicación internacional corresponde a la WO2008067177 del 2008-06-05.

2.2. La solicitud colombiana 09 055461 objeto de la presente oposición se refiere a un método de tratamiento del abuso, adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (1):



en donde: R1 y R2, cada uno independientemente, se seleccionan del grupo que consiste en hidrógeno y alquilo de C1-4; o una sal farmacéuticamente aceptable del mismo; solo o en una terapia combinada con al menos un agente contra la adicción. El método de tratamiento del abuso, adicción o dependencia del alcohol, según la solicitud comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A):



o una sal farmacéuticamente aceptable del mismo, método en donde el compuesto de fórmula (I-A) o su sal farmacéuticamente aceptable es una sal monosulfato cristalina de un compuesto de fórmula (I-A) y donde el abuso, adicción o

dependencia del alcohol es el abuso del alcohol o la dependencia del alcohol, y el ansia de alcohol.

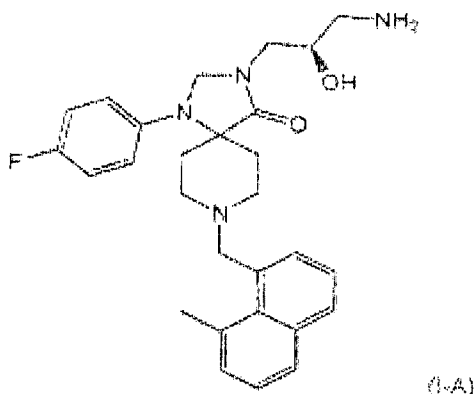
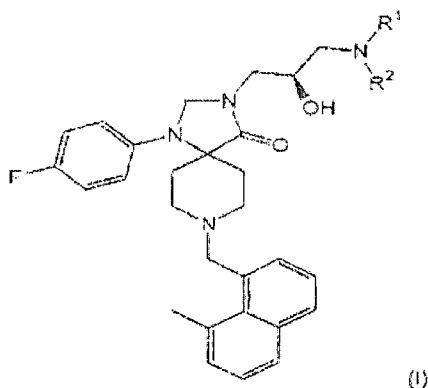
2.3. En primera instancia, se debe advertir que en el capítulo reivindicatorio de la solicitud objeto de la presente oposición, se hace referencia a los usos de la composición en la medicina, no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso no sería patentable.

2.4. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*, tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: US7081463 publicada el 25 de mayo de 2006.

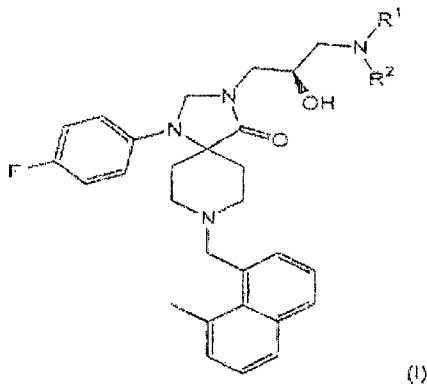
2.5. Ahora bien, el documento D1, se refiere a derivados de 1, 3, 8-triazaspiro [4.5] decan-4-ona hidroxil alquilo sustituidos, útiles en el tratamiento de los trastornos y condiciones mediadas por el receptor de ORL-1 acoplado a la proteína G. Más

concretamente, los compuestos revelados en dicho documento D1 son útiles en el tratamiento de los trastornos y las enfermedades como ansiedad, depresión, pánico, demencia, manía, trastorno bipolar, abuso de sustancias, dolor neuropático, el dolor agudo, dolor de la migraña crónica, asma, tos, psicosis, esquizofrenia, epilepsia, hipertensión, obesidad, trastornos alimentarios, ansiedad, diabetes, arritmia cardíaca, síndrome del intestino irritable, enfermedad de Crohn, incontinencia urinaria, trastornos suprarrenales, el trastorno por déficit de atención (ADD), déficit de atención con hiperactividad (TDAH), enfermedad de Alzheimer, para mejorar la cognición o la memoria y para la estabilización del estado de ánimo. El Documento D1, particularmente en los ejemplos 34 y 50 describe el uso de compuestos pertenecientes a las fórmulas I, e IA:

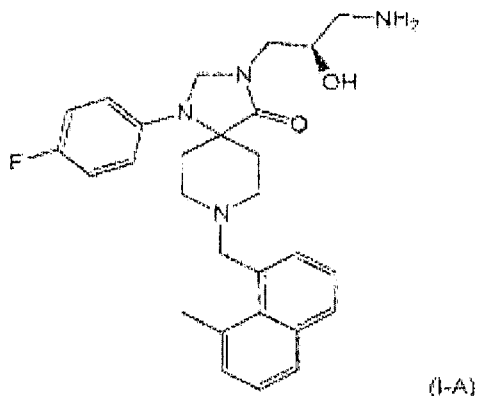


y una lista de sales, tales como la sal de sulfato. Adicionalmente según dicho documento D1, el tratamiento al que está dirigido, se puede aplicar a una lista de trastornos, entre los que se encuentran el abuso de sustancias y el deseo (ansia). Los compuestos 3- (3-Amino-2-(R)-hydroxy-propyl)- 1- (4-fluoro-phenyl)- 8 -(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one y 3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1- (4-fluoro-phenyl)-8- (8-methyl-naphthalen-1-ylmethyl)-1, 3, 8-triaza-spiro [4.5]decan-4-one, correspondientes a los ejemplos 34 y 50 se describen adicionalmente como ligados del receptor ORL-1 acoplado a la proteína G (ORL-1 G protein receptor ligands). La solicitud objeto de la presente oposición no es novedosa pues lo reclamado ya era parte de arte anterior.

2.6. Tomando el documento D1 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1 por sí solo, concebir un método de tratamiento del abuso, adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I):



y/o una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A):



o una sal farmacéuticamente aceptable del mismo, teniendo en cuenta que dichos compuestos son conocidos para el tratamiento de abuso y ansia de sustancias en general. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 055461 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con ninguno de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARENCIA DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- “Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, 28 de noviembre de 2006 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, un método de tratamiento del abuso,

adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), en donde: R1 y R2, cada uno independientemente, se seleccionan del grupo que consiste en hidrógeno y alquilo de C1-4; o una sal farmacéuticamente aceptable del mismo; solo o en una terapia combinada con al menos un agente contra la adicción. El método de tratamiento del abuso, adicción o dependencia del alcohol, según la solicitud comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A), o una sal farmacéuticamente aceptable del mismo, método en donde el compuesto de fórmula (I-A) o su sal farmacéuticamente aceptable es una sal monosulfato cristalina de un compuesto de fórmula (I-A) y donde el abuso, adicción o dependencia del alcohol es el abuso del alcohol o la dependencia del alcohol, y el ansia de alcohol; sobre lo cual busca protección en el capítulo reivindicatorio.

- 2.8.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- “*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*”. A la fecha de prioridad, 28 de noviembre de 2006, a partir del documento D1 por sí solo, un experto en la materia puede llegar de manera evidente a tomar compuestos conocidos para el tratamiento de abuso y ansia de sustancias en general y concebir un método de tratamiento del abuso, adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), o administrar a un sujeto en necesidad

del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A); sobre lo cual busca protección en el capítulo reivindicatorio.

2.8.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, en el capítulo reivindicatorio se reclaman usos y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumple con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con ninguno de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada “METODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCION Y DEPENDENCIA DEL ALCOHOL”, cuyos titulares son JANSSEN PHARMACEUTICA N.V., solicitud Colombiana que apareció

publicada en la Gaceta de la Propiedad Industrial N° 619 del 19 de agosto de 2010.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US7081463 publicada el 25 de mayo de 2006.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

14

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-055461- -00006-0000

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Act. 400 OPOSIOBSERVTER Folios: 92

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 97,375
FECHA : NOVIEMBRE 17 DE 2010

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	392197421	17/11/2010	2,350,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo, a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 09 055.461, titulada "**MÉTODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCIÓN Y DEPENDENCIA DEL ALCOHOL**", cuyo titular es **JANSSEN PHARMACEUTICA N.V.**, publicada en la gaceta No. 619 del 20 de agosto de 2010.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativamente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 3 días del mes de Noviembre de 2010.


PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

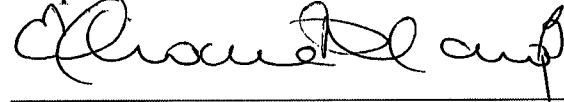
Representante Legal

APROBADO

3 DE NOV. 2010

JURIDICA

Acepto:



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

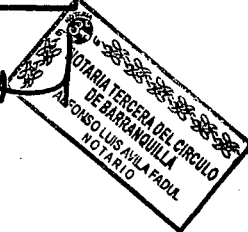
NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO

Ante el Notario Tercero de Barranquilla se presento:
WALTER TANAKA TATERAWA

identificado con: CC 16.251.923 PALMERAS

Y declaro que el contenido del anterior Documento es cierto
y suya la firma que lo respalda.

Barranquilla: 5 NOV. 2010





***** Pag. 1

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.
NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996,
otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta
Camara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del
libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.



***** Pag. 2

CAMARA DE COMERCIO
DE BARRANQUILLA

09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.
NIT: 890.106.527-5.

farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

CAPITAL

Autorizado

*****2,000,000,000 *****2,000,000,000*****1,000

Suscrito

*****1,234,071,000 *****1,234,071 *****1,000

Pagado

*****1,234,071,000 *****1,234,071 *****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se

***** C O N T I N U A *****



***** Pag. 3

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5.

ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

CERTIFICA

CAMARA DE
COMERCIO

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

CC.*****7,463,982

CC.*****7,461,324

CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot
2. Minski Deitel Daniel
3. Minski Sharon

CC.*****72,219,541

PA.*990,212,082,805

CERTIFICA

***** CONTINUA *****



***** Pag. 4

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
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***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.
NIT: 890.106.527-5.

Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel

CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre
Suplente del Revisor Fiscal.
Duarte Diaz David

Identificación

CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo, y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, 3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, 3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condición de Presidente y Representante Legagl de la sociedad PROCAPS S.A., Del presidente debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que representen a la sociedad PROCAPS S.A, ante todo tipo de autoridades administrativas y jurisdiccionales, en asuntos de naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y presentar demandas, requerimientos, recursos, pedir y aportar pruebas, recibir, notificarse, ejercer la accion de tutela, tramitar incidente de desacato, comparecer en los procesos que cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de conciliar, por tanto pueden llegar a acuerdos conciliatorios, transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningún momento quede sin representacion legal de la sociedad. PODERES ESPECIALES: a.- Se confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para

***** C O N T I N U A *****

Barranquilla, 07 de Octubre de 2010 Hr:10:00:56



***** Pag. 5

CAMARA DE COMERCIO
DE BARRANQUILLA

09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ----- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ----- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ----- VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ----- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----- amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA ----- CC.No.8.715.941, para que en nombre y representación de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto, quedan facultados para firmarlas, como también los demás documentos relacionados con ellas, ----- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al señor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de ----- PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los trámites o registros de Comercio ----- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ----- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----- representación de PROCAPS S.A.; endosen los títulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----- (1.000.000.000.00) M.L. CUARTO: El representante legal de la ----- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ----- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condición de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ----- publico Poder especial Amplio y Suficiente a la doctora MILENA -----

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5.

ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda ----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de
2010 bajo el Nro 4,201 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
quien obra en el caracter de Presidente y/o Representante legal de
la sociedad PROCAPS S.A., que por medio de este instrumento -----
publico, otorga Poder Especial Amplio y Suficiente a la Doctora ---
MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para
que en nombre y representacion de la sociedad, Endose las Facturas
Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE
PESOS (\$1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa,
queda facultada para realizar todo acto o tramite necesario para el
cabal cumplimiento del presente mandato.-----

C E R T I F I C A CAMARA DE

Que por Documento Privado del 10 de Junio de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de
2010 bajo el Nro 4,228 del libro respectivo,-----
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su
condicion de Presidente y representante legal de PROCAPS S.A., ----
confiere poder especial, amplio y suficiente al señor RICARDO DORADO
HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante
el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que
gestione, tramite o presente las diferentes solicitudes y -----
peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado
para presentar, gestionar, tramitar y firmar las diferentes -----
solicitudes y peticiones de la empresa, segun la competencia de ----
estas entidades, como tambien presentar y firmar todo los -----
documentos relacionados con estas solicitudes, notificarse de -----
cualquier acto administrativo que expidan, aportar y solicitar las
pruebas que sean necesarias, desistir, y en general a realizar todo
tramite o acto necesario de tal forma que la sociedad en ningun ---
momento quede sin representacion legal ante estas entidades, en --
cumplimiento fiel al mandato otorgado.-----

C E R T I F I C A

Que por Documento Privado del 03 de Agosto de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto
de 2010 bajo el Nro 4,258 del libro respectivo,-----
consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.-----
NIT: 890.106.527-5.

vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las ----- facultades otorgadas por los Estatutos Sociales, todo lo cual ----- demuestro con el certificado de existencia y representación legal expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de ----- edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes ----- actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS ----- (\$1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones ----- Cambiarias, Aduaneras y Tributarias a las que esta obligada la ----- sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda ----- facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el ----- cabal cumplimiento del presente mandato.-----

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Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 30 de Marzo de 2010.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

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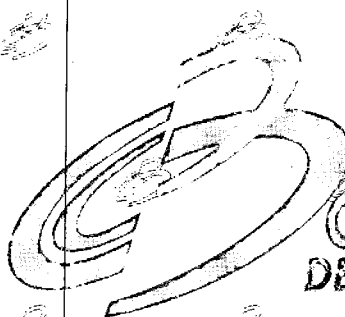
Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

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NIT: 890.106.527-5.

Procaps



CAMARA DE
COMERCIO
DE BARRANQUILLA

Anexo I



US007081463B2

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

(10) **Patent No.:** **US 7,081,463 B2**
(45) **Date of Patent:** **Jul. 25, 2006**

(54) **HYDROXY ALKYL SUBSTITUTED
1,3,8-TRIAZASPIRO[4.5]DECAN-4-ONE
DERIVATIVES USEFUL FOR THE
TREATMENT OF ORL-1 RECEPTOR
MEDIATED DISORDERS**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/656,934**

(22) Filed: **Sep. 5, 2003**

(65) **Prior Publication Data**
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Related U.S. Application Data
(60) Provisional application No. 60/409,134, filed on Sep.
9, 2002.
(51) **Int. Cl.**
H61K 31/438 (2006.01)
C07D 401/04 (2006.01)
(52) **U.S. Cl.** **514/278; 546/18**
(58) **Field of Classification Search** **546/18;**
514/278
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS
3,238,216 A 3/1966 Janssen
3,839,340 A * 10/1974 Scharpf 546/20
4,329,353 A * 5/1982 Stokbroekx et al. 514/278
5,739,336 A 4/1998 Weinhardt et al.
6,043,366 A * 3/2000 Adam et al. 546/16
6,060,482 A 5/2000 Heine et al.
6,071,925 A 6/2000 Adam et al.
6,113,527 A 9/2000 Adam et al.
6,262,066 B1 7/2001 Tulshian et al.
6,277,991 B1 * 8/2001 Hohlweg et al. 546/20
6,777,421 B1 8/2004 Jordan et al.
2003/0109539 A1 6/2003 Jordan et al.

FOREIGN PATENT DOCUMENTS
EP 921125 B1 6/1999
EP 0997464 * 3/2000
EP 997464 A1 5/2000
JP 2000-169476 6/2000
WO WO 93/12789 A1 7/1993

WO WO 95/07294 A1 3/1995
WO 99/59997 * 11/1999
WO WO 99/59997 A1 11/1999
WO WO 00/06545 A1 2/2000
WO WO 01/07050 A1 2/2001
WO WO 01/36418 A1 5/2001
WO WO 01/39723 A2 6/2001
WO WO 01 46192 A 6/2001
WO WO 01/96337 A1 6/2001
WO WO 03/010168 A1 7/2001
WO WO 01/94346 A1 12/2001
WO WO 02/83673 A1 10/2002
WO WO 02/085355 A1 10/2002

OTHER PUBLICATIONS

PCT Search Report dated Feb. 18, 2004 for PCT APPLN.
No. PCT/US03/27956.

Calo, G. et al., "Pharmacological Profile of Nociceptin/
Orphanin FQ Receptors" Clinical and Experimental Phar-
macology and Physiology (2002), 29, 223-228.

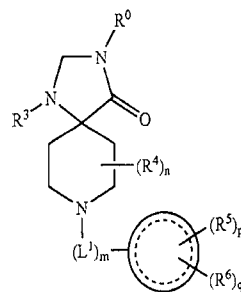
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(57) **ABSTRACT**

The present invention is directed to novel hydroxy alkyl
substituted 1,3,8-triazaspiro[4.5]decan-4-one derivatives of
the general formula



wherein all variables are as defined herein, useful in the
treatment of disorders and conditions mediated by the
ORL-1 G-protein coupled receptor. More particularly,
the compounds of the present invention are useful in
the treatment of disorders and conditions such as anxi-
ety, depression, panic, dementia, mania, bipolar disor-
der, substance abuse, neuropathic pain, acute pain,
chronic pain, migraine, asthma, cough, psychosis,
schizophrenia, epilepsy, hypertension, obesity, eating
disorders, cravings, diabetes, cardiac arrhythmia, irri-
table bowel syndrome, Crohn's disease, urinary incontinence,
adrenal disorders, attention deficit disorder
(ADD), attention deficit hyperactivity disorder
(ADHD), Alzheimer's disease, for improved cognition
or memory and for mood stabilization.

15 Claims, No Drawings

OTHER PUBLICATIONS

Chalon, S. et al "Iodoethylspiperone, a New Potential Agent for Exploration of Central Dopamine D₂ Receptors: Synthesis and Preliminary *In Vivo* Study" Nucl. Med. Bio. (1990), 17(4), 389-395.

Kiesewetter, D. et al., "Syntheses and D₂ Receptor Affinities of Derivatives of Spiperone Containing Aliphatic Halogens" Appl. Radiat. Isot. (1986), 37(12), 1181-1188.

Poulain, R. et al., "From Hit to Lead. Analyzing Structure—Profile Relationship" J. Med. Chem. (2001), 44, 3391-3401.

Poulain, R. et al., "From Hit to Lead. Combining Two Complementary Methods for Focused Library Design. Application to μ Opiate Ligands" J. Med. Chem. (2001), 44, 3378-3390.

Röver S. et al., "High-Affinity, Non-Peptide Agonists for the ORL1 (Orphanin FQ/Nociceptin) Receptor" J. Med. Chem. (2000), 43, 1329-1338.

Satyamurthy, N. et al., "3-(2-[¹⁸F]Fluoroethyl)spiperone, a Potent Dopamine Antagonist: Synthesis, Structural Analysis

and *In-vivo* Utilization in Humans" Appl. Radiat. Isot. (1990) 41(2), 113-129.

U.S. Appl. No. 10/909,858, Ortho-McNeil Pharmaceutical, Inc.

Ronzoni, Silvano et al., "Lead generation and lead optimization approaches in the discovery of selective, non-peptide ORL-1 receptor agonists and antagonists," Exp. Opin. Ther. Patents, 2001, (11)4, pp. 525-546.

Zaverl, Nurulain, "Peptide and nonpeptide ligands for the nociceptin/orphanin FQ receptor ORL1: Research tools and potential therapeutic agents," Life Sciences 73 (2003), pp. 663-678.

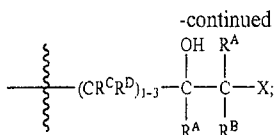
Jenck, Francois et al., "A synthetic agonist at the orphanin FQ/nociceptin receptor ORL1: Anxiolytic profile in the rat," PNAS, Apr. 25, 2000, vol. 97, No. 9, pp. 4938-4953.

Thomsen, Chrisian et al., "(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]-dec-3-yl)-acetic acid methyl ester (NNC 63-0532) is a novel potent nociceptin receptor agonist," British Journal of Pharmacology (2000) 131, 903-908.

* cited by examiner

US 7,081,463 B2

3



each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4} alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, arC_{1-4} alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

X is selected from the group consisting of $-\text{NR}^1\text{R}^2$, $-\text{C}(\text{O})-\text{NR}^1\text{R}^2$, $-\text{NR}^1-\text{C}(\text{O})-\text{R}^2$, $-\text{OR}^1$, $-\text{SR}^1$, $-\text{SOR}^1$, $-\text{SO}_2\text{R}^1$, $-\text{S}-(\text{C}_{2-4}\text{alkyl})-\text{NR}^1\text{R}^2$, $-\text{S}-(\text{C}_{2-4}\text{alkyl})-\text{NR}^1-\text{C}(\text{O})\text{O}-\text{C}(\text{CH}_3)_3$, $-\text{SO}-(\text{C}^1\text{alkyl})-\text{NR}^1\text{R}^2$ and $-\text{SO}_2-(\text{C}_{1-4}\text{alkyl})-\text{NR}^1\text{R}^2$; wherein the alkyl portion of the $-\text{S}-(\text{C}_{2-4}\text{alkyl})-\text{NR}^1\text{R}^2$, $-\text{SO}-(\text{C}^1\text{alkyl})-\text{NR}^1\text{R}^2$ or $-\text{SO}_2-(\text{C}_{1-4}\text{alkyl})-\text{NR}^1\text{R}^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxyc₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxycarbonyl or $-\text{CONR}^1\text{R}^2$.

each R¹ and R² is independently selected from the group consisting of hydrogen, C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, cycloalkyl, cycloalkyl-C₁₋₄alkyl, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl-C₁₋₄alkyl, aryl, arC₁₋₄alkyl, arC₁₋₄alkoxy, heteroaryl, heteroaryl-C₁₋₄alkyl, heterocycloalkyl, heterocycloalkyl-C₁₋₄alkyl, —C(O)—C₁₋₆alkyl, —C(O)-aryl, —C(O)-arC₁₋₄alkyl, —C(O)-heteroaryl, —C(O)-heterocycloalkyl, —C(O)O-cycloalkyl and —C(O)O-aryl, —C(O)O-arC₁₋₄alkyl, —C(O)O-(partially unsaturated carbocyclyl), C(O)-heteroaryl, —C(O)O-heterocycloalkyl; wherein the C₁₋₈alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC₁₋₄alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, C(O)—C₁₋₄alkyl, C₁₋₄alkoxycarbonyl, N(R^E)₂, N(R^E)₂—C₁₋₄alkyl, N(R^E)—C(O)C(CH₃)₃, —C₁₋₄alkyl-N(R^E)—C(O)O—C₁₋₄alkyl and —N(R^E)—C(O)O—C₁₋₄alkyl, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylaminosulfonyl or C₁₋₆alkylthio;

alternatively when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₆alkyl, hydroxy substituted C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂, aryl, arC₁₋₆alkyl, heteroaryl, heterocycloalkyl, di(C₁₋₆)alkylamino-carbonyl, C₁₋₆alkoxycarbonyl-N(R^E)— or arylamino-C₁₋₆alkyl; wherein the aryl, arC₁₋₆alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₆alkyl, C₁₋₆alkoxy, trifluoromethyl, trifluoro-

4

romethoxy, nitro, cyano, $N(R^E)_2$, phenyl or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R³ is selected from the group consisting of aryl, arC₁₋₆alkyl and heteroaryl; wherein the aryl, arC₁₋₆alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or N(R^E)₂;

n is an integer from 0 to 2;

R⁴ is selected from the group consisting of hydroxy, C₁₋₄alkyl and hydroxy substituted C₁₋₄alkyl;

15 m is an integer from 0 to 1;

L¹ is selected from the group consisting of C₁₋₆alkyl and C₃₋₆alkenyl; wherein the double bond of the C₃₋₆alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C₁₋₆alkyl or C₃₋₆alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C₁₋₆alkyl, fluorinated C₁₋₆alkyl or C₁₋₆alkoxy;



³⁰ selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

35 R⁵ is selected from the group consisting of hydroxy, carboxy, halogen, C₁₋₆alkyl, hydroxy substituted C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, NR¹R², trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxycarbonyl, —SO—NR¹R², —SO₂—NR¹R² and —C(O)—NR¹R².

40 q is an integer from 0 to 1;

40) R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;
 L^2 is selected from the group consisting of $-C_{1-6}alkyl-$,
 $-C_{2-4}alkenyl-$, $-C_{2,6}alkynyl-$, $-O-$, $-S-$, $-NH-$,
 $-N(C_{1-4}alkyl)-$, $-C_{1,6}alkyl-O-$, $-C_{1,6}alkyl-S-$,
45 $-O-C_{1,6}alkyl-$, $-S-C_{1,6}alkyl-$, $-O-C_{2,6}alkyl-O-$,
 $-S-C_{2,6}alkyl-S-$, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$,
 $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, $-C(O)-$
 $O-$ and $-O-C(O)-$;

R⁷ is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, N(R^E)₂, trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, —SO₂—N(R^E)₂ and —C(O)—N(R^E)₂;

or a pharmaceutically acceptable salt thereof.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. An illustration of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier.

US 7,081,463 B2

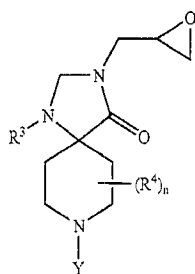
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Exemplifying the invention are methods of treating disorders and conditions mediated by the ORL-1 receptor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

An example of the invention is a method of treating a condition selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Another example of the invention is the use of any of the compounds described herein in the preparation of a medicament for treating: (a) anxiety, (b) depression, (c) panic, (d) mania, (e) dementia, (f) bipolar disorder, (g) substance abuse (h) neuropathic pain, (i) acute pain, (j) chronic pain, (k) migraine, (l) asthma, (m) cough, (n) psychosis, (o) schizophrenia, (p) epilepsy, (q) hypertension, (r) obesity, (s) eating disorders, (t) cravings, (u) diabetes, (v) cardiac arrhythmia, (w) irritable bowel syndrome, (x) Crohn's disease, (uy) urinary incontinence, (z) adrenal disorders, (aa) attention deficit disorder (ADD), (bb) attention deficit hyperactivity disorder (ADHD), (cc) Alzheimer's disease, for (dd) improved cognition, (ee) improved memory and (ff) mood stabilization, in a subject in need thereof.

The present invention is further directed to a compound of formula (E)



wherein

R^3 is selected from the group consisting of aryl, arC₁₋₆alkyl and heteroaryl; wherein the aryl, arC₁₋₆alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

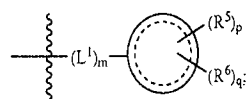
wherein each R^E is independently selected from hydrogen or C₁₋₄alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C₁₋₄alkyl and hydroxy substituted C₁₋₄alkyl;

Y is selected from the group consisting of hydrogen, C₁₋₄alkyl, t-butoxycarbonyl and

6



m is an integer from 0 to 1;

L^1 is selected from the group consisting of C₁₋₆alkyl and C₃₋₆alkenyl;

wherein the double bond of the C₃₋₆alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C₁₋₆alkyl or C₃₋₆alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C₁₋₆alkyl, fluorinated C₁₋₆alkyl or C₁₋₆alkoxy;



is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C₁₋₆alkyl, hydroxy substituted C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, NR^1R^2 , trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, $-SO-NR^1R^2$, $-SO_2-NR^1R^2$ and $-C(O)-NR^1R^2$;

q is an integer from 0 to 1;

R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

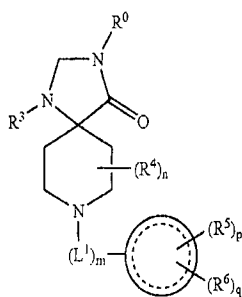
L^2 is selected from the group consisting of $-C_{1-6}$ alkyl-, $-C_{2-6}$ alkenyl-, $-C_{2-6}$ alkynyl-, $-O-$, $-S-$, $-NH-$, $-N(C_{1-4}alkyl)-$, $-C_{1-6}alkyl-O-$, $-C_{1-6}alkyl-S-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-O-C_{2-6}alkyl-O-$, $-S-C_{2-6}alkyl-S-$, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, $-C(O)-O-$ and $-O-C(O)-$;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides hydroxy alkyl substituted 1,3,8-triazaspiro[4.5]decan-4-one derivatives useful for the treatment of disorders and conditions mediated by the ORL-1 receptor. More particularly, the compounds of the present invention are of the general formula (I)



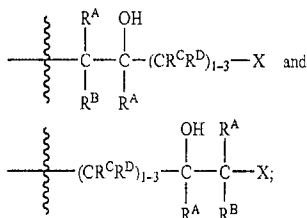
wherein R^0 , R^3 , n , R^4 , m , L^1 ,



p , R^5 , q and R^6 are as herein defined, or a pharmaceutically acceptable salt thereof. The compounds of formula (I) are useful in the treatment of disorders mediated by the ORL-1 receptor. The compound of formula (I) are further useful for the treatment of disorders associated with the adrenal gland.

More particularly, the compound of formula (I) are useful in the treatment of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization. Preferably, the compounds of formula (I) are useful in the treatment of anxiety, depression, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, cough, hypertension, cardiac arrhythmia, irritable bowel syndrome and Crohn's disease.

In an embodiment of the present invention are compounds of formula (I) wherein R^0 is selected from the group consisting of



each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4} alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, arC_{1-4} alkyl, heteroaryl or heterocycloalkyl substituent is optionally sub-

stituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxy C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxycarbonyl or $-CONR^1R^2$;

each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, cycloalkyl, cycloalkyl- C_{1-4} alkyl, partially unsaturated carbocyclyl, aryl, arC_{1-4} alkyl, arC_{1-4} alkoxy, heteroaryl, heteroaryl- C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl- C_{1-4} alkyl, $-C(O)-C_{1-6}alkyl$, $-C(O)-aryl$, $-C(O)-arC_{1-4}alkyl$, $-C(O)-heteroaryl$ and $-C(O)-heterocycloalkyl$; wherein the C_{1-8} alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC_{1-4} alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $C(O)-C_{1-4}alkyl$, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$, $N(R^E)-C(O)C(CH_3)_3$, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylamino-sulfonyl or $C_{1-4}alkylthio$;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, $arC_{1-4}alkyl$, heteroaryl, heterocycloalkyl, $di(C_{1-6}alkylamino-carbonyl)$, $t-butoxycarbonyl$ or $arylamino-C_{1-4}alkyl$; wherein the aryl, $arC_{1-4}alkyl$, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R^3 is selected from the group consisting of aryl, $arC_{1-6}alkyl$ and heteroaryl; wherein the aryl, $arC_{1-6}alkyl$ or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4} alkyl and hydroxy substituted $C_{1-4}alkyl$;

m is an integer from 0 to 1;

US 7,081,463 B2

9

L^1 is selected from the group consisting of C_{1-6} alkyl and C_{3-6} alkenyl; wherein the double bond of the C_{3-6} alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6} alkyl or C_{3-6} alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6} alkyl, fluorinated C_{1-6} alkyl or C_{1-6} alkoxy;



is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, cyano, NR^1R^2 , trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $SO_2NR^1R^2$, $SO_2NR^1R^2$ and $C(O)NR^1R^2$;

q is an integer from 0 to 1;

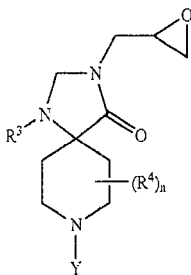
R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

L^2 is selected from the group consisting of $-C_{1-6}$ alkyl-, $-C_{2-4}$ alkenyl-, $-C_{2-6}$ alkynyl-, $-O-$, $-S-$, $-NH-$, $-N(C_{1-4}alkyl)-$, $-C_{1-6}alkyl-O-$, $-C_{1-6}alkyl-S-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-O-C_{2-6}alkyl-O-$, $-S-C_{2-6}alkyl-S-$, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, $-C(O)-O-$ and $-O-C(O)-$;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $SO_2N(R^E)_2$ and $C(O)N(R^E)_2$;

and pharmaceutically acceptable salts thereof.

In an embodiment of the present invention are compounds of the formula (E)



wherein R^3 , n, R^4 , and Y are as herein defined, or a pharmaceutically acceptable salt thereof. The compounds of formula (E) are useful as intermediates in the preparation of compounds of formula (I).

In an embodiment of the present invention are compounds of formula (E) wherein R^3 is selected from the group consisting of aryl, arC_{1-6} alkyl and heteroaryl; wherein the aryl, arC_{1-6} alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from

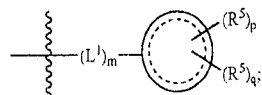
10

halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$; wherein each R^E is independently selected from hydrogen or C_{1-4} alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4} alkyl and hydroxy substituted C_{1-4} alkyl;

Y is selected from the group consisting of hydrogen, C_{1-4} alkyl, t-butoxycarbonyl and



m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6} alkyl and C_{3-6} alkenyl; wherein the double bond of the C_{3-6} alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6} alkyl or C_{3-6} alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6} alkyl, fluorinated C_{1-6} alkyl or C_{1-6} alkoxy;



is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, cyano, NR^1R^2 , trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $SO_2NR^1R^2$, $SO_2NR^1R^2$ and $C(O)NR^1R^2$;

q is an integer from 0 to 1;

R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

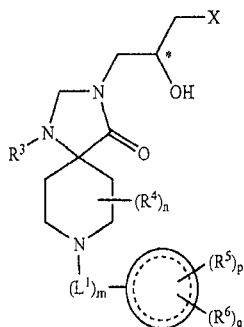
L^2 is selected from the group consisting of $-C_{1-6}$ alkyl-, $-C_{2-4}$ alkenyl-, $-C_{2-6}$ alkynyl-, $-O-$, $-S-$, $-NH-$, $-N(C_{1-4}alkyl)-$, $-C_{1-6}alkyl-O-$, $-C_{1-6}alkyl-S-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-O-C_{2-6}alkyl-O-$, $-S-C_{2-6}alkyl-S-$, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, $-C(O)-O-$ and $-O-C(O)-$;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $SO_2N(R^E)_2$ and $C(O)N(R^E)_2$;

and pharmaceutically acceptable salts thereof.

In an embodiment of the present invention are compounds of the formula (Ia)

11



wherein X, R³, n, R⁴, m, L¹,

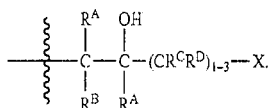


R⁵, q and R⁶ are as herein defined, or a pharmaceutically acceptable salt thereof. The compounds of formula (I) are useful in the treatment of disorders mediated by the ORL-1 receptor.

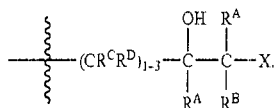
In an embodiment of the present invention is a compound of formula (I) wherein the binding of the compound to the ORL-1 receptor is 10 fold greater than the binding of the compound to the μ opioid (OP-3) receptor. In another embodiment of the present invention is a compound of formula (I) wherein the binding of the compound to the ORL-1 receptor is 100 fold greater, preferably 500 fold greater, more preferably 1000 fold greater, than the binding of the compound to the μ opioid (OP-3) receptor.

In an embodiment of the present invention is a compound of formula (I) wherein the compound's measured IC₅₀ to the ORL-1 receptor is less than or equal to about 100 nM, preferably less than or equal to about 50 nM. In another embodiment of the present invention is a compound of formula (I) wherein the compound's measured K_i to the ORL-1 receptor is less than or equal to about 100 nM, preferably less than or equal to about 50 nM.

In an embodiment of the present invention R⁰ is



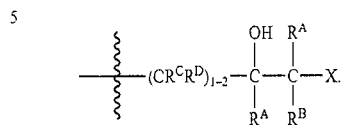
In another embodiment of the present invention, R⁰ is



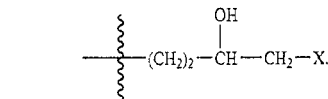
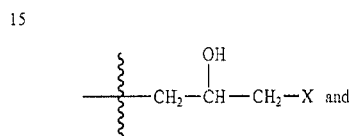
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In yet another embodiment of the present invention, R⁰ is

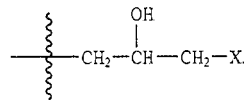
(1a)



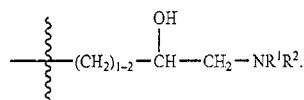
Preferably, R⁰ is selected from the group consisting of



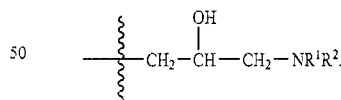
More preferably, R⁰ is



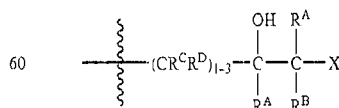
In yet another embodiment of the present invention, R⁰ is



Preferably, R⁰ is

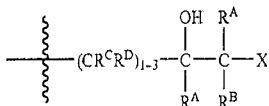


In an embodiment of the present invention, the hydroxy group on the



group is present in the R stereo-configuration. In another embodiment of the present invention, the hydroxy group on the

13



group is present in the S stereo-configuration.

In an embodiment of the present invention R^A and R^B are each independently selected from hydrogen, methyl and ethyl, preferably R^A and R^B are each hydrogen. In another embodiment of the present invention R^C and R^D are each independently selected from hydrogen and C_{1-4} alkyl, preferably R^C and R^D are each hydrogen. In yet another embodiment of the present invention R^E is selected from the group consisting of hydrogen, methyl and ethyl, preferably R^E is hydrogen.

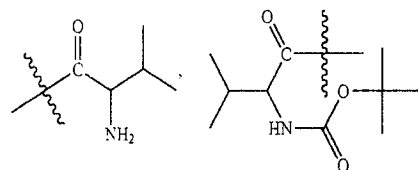
In an embodiment of the present invention X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2-OR^1$, $-SR^1$, $-SO-R^1$, $-SO^2-R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$, $-SO^2-(C_{1-4}alkyl)-NR^1R^2$ wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{1-4}alkyl)-NR^1-C(O)-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO^2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one to two substituents independently selected from C_{1-4} alkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxycarbonyl or carboxy. Preferably, X is selected from the group consisting of $-NR^1R^2$, $-OR^1$, $-SR^1$, $-S-(C_{2-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$, $-S-(C_{2-4}alkyl)-NR^1R^2$ wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$ or $-S-(C_{1-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$ group is optionally substituted with a carboxy or C_{1-4} alkoxycarbonyl group. More preferably, X is selected from the group consisting of $-NR^1R^2$, $-OR^1$, $-SR^1$, $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$ and $-S-CH_2CH(CO_2H)-NH-C(O)O-C(CH_3)_3$. More preferably still, X is selected from the group consisting of $-NR^1R^2$, $-SR^1$ and $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$.

In an embodiment of the present invention R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, aryl, $arC_{1-4}alkyl$, $arC_{1-4}alkyloxy$, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl, $C(O)-C_{1-4}alkyl$ and $-C(O)-heteroaryl$; wherein the $C_{1-4}alkyl$, aryl, $arC_{1-4}alkyl$, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$, $N(R^E)-C(O)OC(CH_3)_3$, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or $C_{1-4}alkylthio$. Preferably, In an embodiment of the present invention R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, aryl, $arC_{1-4}alkyl$, $arC_{1-4}alkyloxy$, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl, $C(O)-C_{1-4}alkyl$ and $-C(O)-heteroaryl$; wherein the $C_{1-4}alkyl$, aryl, $arC_{1-4}alkyl$, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, $C_{1-4}alkyl$, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$, $N(R^E)-C(O)OC(CH_3)_3$, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or $C_{1-4}alkylthio$.

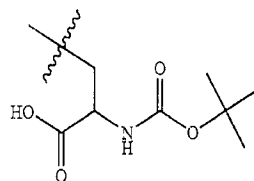
14

In another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, $arC_{1-4}alkyl$, C_{1-4} alkoxycarbonyl and $C(O)-C_{1-4}alkyl$; wherein the $C_{1-4}alkyl$, $arC_{1-4}alkyl$ or aryl group, whether alone or part of a substituent group, is optionally substituted with one to two substituents independently selected from carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$ or $N(R^E)-C(O)OC(CH_3)_3$. Preferably, R^1 is selected from the group consisting of hydrogen, $C_{1-4}alkyl$, $arC_{1-4}alkyl$ and $C(O)-C_{1-4}alkyl$; wherein the $C_{1-4}alkyl$, $arC_{1-4}alkyl$ or aryl group, whether alone or part of a substituent group, is optionally substituted with one to two substituents independently selected from carboxy, $C_{1-4}alkyl$, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$ or $N(R^E)-C(O)OC(CH_3)_3$.

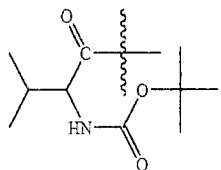
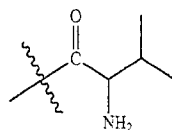
In another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, amino-n-propyl, dimethylaminoethyl, benzyl, phenylethyl, 4-methyl-benzyl,



2-(3,4-dimethoxy-phenyl)ethyl, 3-methylphenyl, 2-amino-2-methoxycarbonyl-ethyl, ethoxy-carbonyl-methyl, t-butoxycarbonyl, and



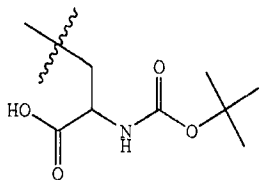
Preferably, R^1 is selected from the group consisting of hydrogen, methyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, 4-methyl-benzyl,



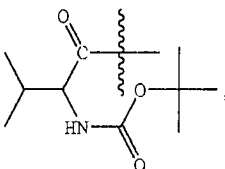
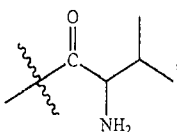
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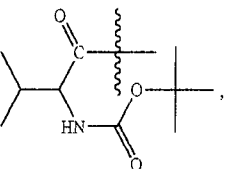
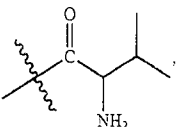
2-(3,4-dimethoxy-phenyl)ethyl, 3-methylphenyl, 2-amino-2-methoxycarbonyl-ethyl and



In another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl,



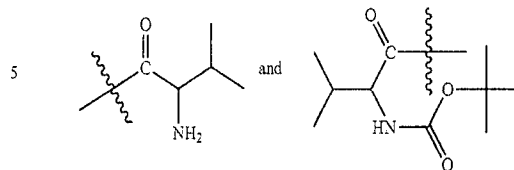
3-methyl-phenyl, 2-(3,4-dimethoxyphenyl)-ethyl, ethoxycarbonyl-methyl, dimethylamino-ethyl and 2-amino-2-methoxycarbonyl-ethyl. Preferably, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl,



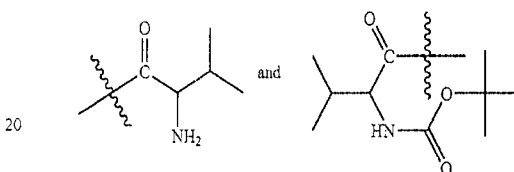
3-methyl-phenyl and 2-amino-2-methoxycarbonyl-ethyl.

In yet another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl, 2-(3,4-dimethoxyphenyl)-ethyl, dimethylamino-ethyl, ethoxy-carbonyl-methyl,

16



Preferably, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl,



In another embodiment of the present invention R^1 is selected from the group consisting of hydrogen, t-butoxycarbonyl, 2-(3,4-dimethoxyphenyl)-ethyl, 1-(3,4-dimethoxyphenyl)-n-ethyl and amino-n-propyl. In yet another embodiment of the present invention R^1 is selected from the group consisting of hydrogen, t-butoxycarbonyl and amino-n-propyl.

In an embodiment of the present invention R^2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, cycloalkyl, cycloalkyl- C_{1-4} alkyl, aryl, arC_{1-4} alkyl, arC_{1-4} alkyloxy, partially unsaturated carbocycl, partially unsaturated carbocycl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl- C_{1-4} alkyl, $-C(O)-C_{1-4}$ alkyl, $-C(O)-aryl$, $-C(O)-arC_{1-4}$ alkyl, $-C(O)-heteroaryl$, $-C(O)-heterocycloalkyl$, $-C(O)-O-cycloalkyl$ and $-C(O)-C_{1-4}$ alkyl; wherein the C_{1-4} alkyl, aryl, arC_{1-4} alkyl, partially unsaturated carbocycl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}$ alkyl, $(CH_3)_3COC(O)-N(R^E)-C_{1-4}$ alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl substituted heteroaryl-amino-sulfonyl, $-C(O)-C_{1-4}$ alkyl or C_{1-4} alkylthio. Preferably, R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, cycloalkyl- C_{1-4} alkyl, aryl, arC_{1-4} alkyl, arC_{1-4} alkyloxy, partially unsaturated carbocycl, heteroaryl, heteroaryl- C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl- C_{1-4} alkyl, $-C(O)-C_{1-4}$ alkyl, $-C(O)-aryl$, $-C(O)-arC_{1-4}$ alkyl, $-C(O)-heteroaryl$ and $-C(O)-heterocycloalkyl$; wherein the C_{1-4} alkyl, aryl, arC_{1-4} alkyl, partially unsaturated carbocycl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}$ alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl substituted heteroaryl-amino-sulfonyl, $-C(O)-C_{1-4}$ alkyl or C_{1-4} alkylthio.

In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, C_{1-4} alkyl,

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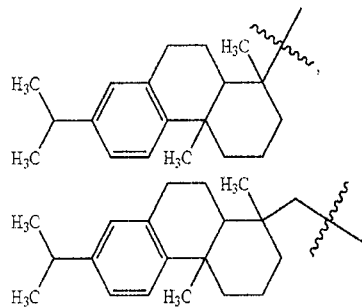
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C₁₋₄alkoxy, cycloalkyl, aryl, arC₁₋₄alkyl, arC₁₋₄alkoxy, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heterocycloalkyl, heterocycloalkyl-C₁₋₄alkyl, cycloalkyl-C₁₋₄alkyl, —C(O)arC₁₋₄alkyl, —C(O)-heteroaryl, —C(OO)-cycloalkyl and —C(O)O—C₁₋₄alkyl; wherein the C₁₋₄alkyl, aryl, arC₁₋₄alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, N(R^E)₂, N(R^E)₂—C₁₋₄alkyl, (CH₃)₃CO—C(O)—N(R^E)—C₁₋₄alkyl, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C₁₋₄alkylthio. Preferably, R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, aryl, arC₁₋₄alkyl, arC₁₋₄alkoxy, partially unsaturated carbocyclyl, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl and —C(O)-heteroaryl; wherein the C₁₋₄alkyl, aryl, arC₁₋₄alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, N(R^E)₂, N(R^E)₂—C₁₋₄alkyl, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C₁₋₄alkylthio.

In an embodiment of the present invention, R² is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, carboxy-methyl, ethoxycarbonylmethyl, 2,2,2-trifluoroethyl, ethoxy, dimethylaminoethyl, t-butoxycarbonylamino-ethyl, n-butyl, t-butyl, n-propyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, di(n-butyl)amino-n-propyl, t-butoxycarbonylamino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, t-butoxycarbonyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 2-aminophenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-cyclohexylphenyl, 4-(aminoethyl)phenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, —CH(CH₃)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)benzyl, 4-(dimethylamino)benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, (2,5-dimethoxy-2,5-dihydro-fur-2-yl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3-

18

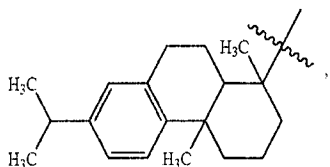
4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 6-methylthio-2-pyridyl-carbonyl, thienyl-methyl, 2-thienylethyl, 4-pyridinyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 1-phenyl-2-(t-butoxycarbonyl)ethyl, —C(O)—C(OCH₃)(CF₃)-phenyl, —C(O)O-(2-isopropyl-5-methyl-cyclohexyl), 1-(4-ethoxycarbonyl-piperidinyl), 2-(3H-imidazol-4-yl)ethyl, 2-(1,2,3,4-tetrahydro-isoquinolinyl), 2-furyl-methyl,



2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl, 2-(2-pyridyl)-ethyl, 2-(6-fluoro-2-indolyl)ethyl and 2-phenyl-cyclopropyl. Preferably, R² is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, carboxy-methyl, ethoxycarbonylmethyl, 2,2,2-trifluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-cyclohexylphenyl, 4-(aminoethyl)phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)benzyl, 4-(dimethylamino)benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, (2,5-dimethoxy-2,5-dihydro-fur-2-yl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 6-methylthio-2-pyridyl-carbonyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 1-phenyl-2-(t-butoxycarbonyl)ethyl, 2-(1,2,3,4-tetrahydro-isoquinolinyl), 2-furyl-methyl,

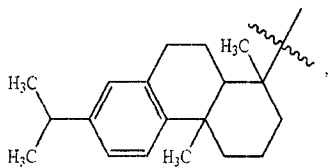
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19



2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl, 2-(2-pyridyl)-ethyl, 2-(6-fluoro-2-indolyl)ethyl and 2-phenyl-cyclopropyl.

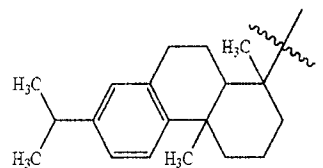
In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, 2,2,2-trifluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl) amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 3,4-dimethoxyphenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-methyl,



2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl and 2-(6-fluoro-2-indolyl)-ethyl. Preferably still, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, 2,2,2-trifluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl,

20

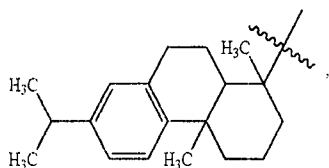
n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-methyl,



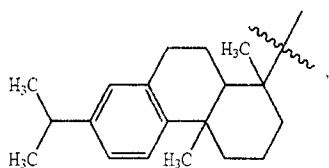
2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl and 2-(6-fluoro-2-indolyl)-ethyl.

In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, ethoxy, dimethylaminoethyl, n-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 3,4-dimethoxyphenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-

propyl, 2-(4-morpholinyl)methyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylene-dioxyphenyl)ethyl, 2-furyl-methyl,



2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl and 2-phenoxy-ethyl. Preferably, R² is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, ethoxy, dimethylaminoethyl, n-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-methyl,



2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl and 2-phenoxy-ethyl.

In an embodiment of the present invention R² is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, t-butoxycarbonylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, —CH(CH₃)-phenyl, 4-pyridinyl, 1-(4-ethoxycarbonyl-piperidinyl) and 2-(3H-imidazol-4-yl)-ethyl.

Preferably, R² is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, —CH(CH₃)-phenyl, 4-pyridinyl and 2-(3H-imidazol-4-yl)-ethyl.

In an embodiment of the present invention, when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, hydroxy substituted C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂, phenyl, arC₁₋₄alkyl, heterocycloalkyl, di(C₁₋₄alkyl)amino-carbonyl, C₁₋₄alkoxycarbonylamino or phenylamino-C₁₋₄alkyl; wherein the phenyl or arC₁₋₄alkyl substituent on the heteroaryl or heterocycloalkyl group is optionally substituted with one or two substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂ or substituted phenyl; wherein the substituents on the phenyl are one to three independently selected from halogen. Preferably, when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂, phenyl, arC₁₋₄alkyl, heterocycloalkyl, di(C₁₋₄alkyl)amino-carbonyl, or phenylamino-C₁₋₄alkyl; wherein the phenyl or arC₁₋₄alkyl substituent on the heteroaryl or heterocycloalkyl group is optionally substituted with one or two substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂ or substituted phenyl; wherein the substituents on the phenyl are one to three independently selected from halogen.

In an embodiment of the present invention, when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a group selected from heterocycloalkyl and heteroaryl; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C₁₋₄alkyl, hydroxy substituted C₁₋₄alkyl, C₁₋₄alkoxy, phenyl, arC₁₋₄alkyl, heterocycloalkyl, C₁₋₄alkoxycarbonyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)amino-carbonyl, t-butoxycarbonyl, t-butoxycarbonylamino or phenylamino-C₁₋₄alkyl; wherein the phenyl or arC₁₋₄alkyl substituent is optionally substituted with one or two substituents independently selected from chloro, trifluoromethyl or chlorophenyl. Preferably, when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a group selected from heterocycloalkyl and heteroaryl; wherein the

heteroaryl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, arC_{1-4} alkyl, heterocycloalkyl, C_{1-4} alkoxycarbonyl, di(C_{1-4} alkyl)amino-carbonyl or phenylamino- C_{1-4} alkyl; wherein the phenyl or arC_{1-4} alkyl substituent is optionally substituted with one or two substituents independently selected from trifluoromethyl or chlorophenyl.

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-morpholinyl, 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-pyrrolidinyl-piperidinyl), 1-(4-phenyl-piperidinyl), 1-(3-hydroxy-piperidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3,5-dimethyl-piperidinyl), 1-(4-dimethylamino-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-t-butoxycarbonylamino-piperidinyl), 1-(2,3-dihydro-1H-pyrrolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-(2,3-dihydro-pyrrolidinyl), 1-(3-hydroxy-pyrrolidinyl), 1-(3-(S)-hydroxy-pyrrolidinyl), 1-piperidinyl, 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl, 1-(2-(phenylamino-methyl)-N-pyrrolidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(3,4-dihydroxy-2,5-bis-hydroxymethyl-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl). Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(2,3-dihydro-1H-pyrrolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-piperidinyl, 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl).

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-morpholinyl, 1-pyrrolidinyl, 1-(2,3-dihydro-pyrrolidinyl), 1-piperidinyl, 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-

pyrrolidinyl). Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-piperidinyl, 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl).

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, 1-imidazolyl, 1-(2,3-dihydro-pyrrolidinyl), and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl). Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-piperidinyl, 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl).

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxypiperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl).

Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxypyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-

US 7,081,463 B2

25

pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl).

In an embodiment of the present invention, n is an integer from 0 to 1, preferably n is 0. In an embodiment of the present invention m is 0. In another embodiment of the present invention m is 1.

In an embodiment of the present invention p is an integer from 0 to 2, preferably p is an integer from 0 to 1. In an embodiment of the present invention q is 0. In another embodiment of the present invention, q is 1.

In an embodiment of the present invention, R^3 is selected from the group consisting of aryl and arC_{1-4} alkyl; wherein the aryl or arC_{1-4} alkyl group is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$. Preferably, R^3 is aryl; wherein the aryl group is optionally substituted with one or more substituents independently selected from halogen. More preferably, R^3 is selected from the group consisting of phenyl and 4-fluorophenyl.

In an embodiment of the present invention, L^1 is C_{1-4} alkyl; wherein the C_{1-4} alkyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-4} alkyl, fluorinated C_{1-4} alkyl or C_{1-4} alkoxy. Preferably, L^1 is unsubstituted C_{1-4} alkyl. More preferably, L^1 is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$ and $-CH_2CH_2-$. More preferably still, L^1 is $-CH_2-$ or $-CH_2CH_2-$.

In an embodiment of the present invention,



is selected from the group consisting of partially unsaturated carbocyclyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl.

In another embodiment of the present invention,



is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphthyl, 2-thienyl, benzothienyl, 4,5,6,7-tetrahydro-benzothienyl, bicyclo[3.1.1]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl. Preferably,



is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl,

26

cyclohexyl, phenyl, 1-naphthyl, 2-naphthyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

In another embodiment of the present invention,



is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-2-yl.

In another embodiment of the present invention,



is selected from the group consisting of cyclooctyl, 1-naphthyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, bicyclo[3.1.1]hepten-2-yl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

In an embodiment of the present invention, R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $-SO-N(R^E)_2$, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$.

In another embodiment of the present invention, R^5 is selected from the group consisting of halogen, C_{1-4} alkyl and trifluoromethyl. Preferably, R^5 is selected from the group consisting of chloro, methyl, n-propyl and trifluoromethyl.

In another embodiment of the present invention, R^5 is selected from the group consisting of methyl, n-propyl, chloro and trifluoromethyl. Preferably, R^5 is selected from the group consisting of methyl, n-propyl and trifluoromethyl. More preferably, R^5 is selected from the group consisting of methyl and n-propyl. In yet another embodiment of the present invention, R^5 is methyl.

In an embodiment of the present invention R^6 is $-(L^2)_0-R^7$. In another embodiment of the present invention, R^6 is $-(L^2)-R^7$ and L is selected from the group consisting of $-C_{1-4}$ alkyl-, $-O-$, $-S-$, $-N(R^E)-$, $-C(O)O-$ and $-O-C(O)-$.

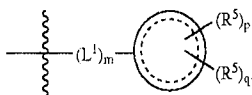
In an embodiment of the present invention, R^7 is selected from the group consisting of cycloalkyl, aryl, heteroaryl and heterocycloalkyl; wherein the aryl, heteroaryl or heterocycloalkyl group is optionally substituted with one to two substituents independently selected from hydroxy, carboxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy or C_{1-4} alkoxycarbonyl. Preferably, R^7 is selected from the group consisting of aryl and heteroaryl. More preferably, R^7 is selected from the group consisting of phenyl and 2-thienyl. More preferably still, R^7 is 2-thienyl.

In an embodiment of the present invention is a compound of formula (I) selected from the group consisting of

8-(R)acenaphthen-1-yl-3-(3-amino-2-(S)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;
8-(R)acenaphthen-1-yl-3-(3-amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R)-Acenaphthen-1-yl-3-(3-dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5] decan-4-one;
 3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5] decan-4-one;
 3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;
 8-(R)-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one;
 3-(3-Amino-2-(R)-hydroxy-propyl)-8-cyclooctyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;
 3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-1-(S)-(3aS)-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1,3,8-triaza-spiro[4.5]decan-4-one;
 1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxy-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;
 1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;
 3-[3-(3-Dimethylamino-propylamino)-2-(R)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one and pharmaceutically acceptable salts thereof.

With regard to compounds of formula (E), in an embodiment of the present invention Y is selected from the group consisting of hydrogen, C_{1-4} alkyl and t-butoxycarbonyl, preferably, C_{1-4} alkyl or t-butoxycarbonyl, more preferably ethyl. In another embodiment of the present invention Y is



Additional embodiments of the present invention, include those wherein the substituents selected for one or more of the variables defined herein (i.e. R^0 , R^3 , n, R^4 , m, L^1 ,



p, R^5 , q, R^6 and Y) are independently selected to be any individual substituent or any subset of substituents selected from the complete list as defined herein.

As used herein, unless otherwise noted, "halogen" shall mean chlorine, bromine, fluorine and iodine.

As used herein, the term "alkyl", whether used alone or as part of a substituent group, include straight and branched alkyl chain, preferably comprising one to eight carbon atoms. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and the like. As used herein, the term "lower alkyl" shall mean a straight or branched alkyl chain comprising one to four carbon atoms. Suitable examples of a lower alkyl group include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like.

As used herein, unless otherwise noted, the term "hydroxy substituted alkyl" shall mean any straight or branched alkyl chain which is substituted with one or more hydroxy groups, for example hydroxymethyl, 1-hydroxy-eth-2-yl, and the like. Preferably, the alkyl chain is substituted with one to three hydroxy groups, more preferably one hydroxy group.

As used herein, unless otherwise noted, "alkoxy" shall denote an oxygen ether radical of the above described straight or branched chain alkyl groups. For example, methoxy, ethoxy, n-propoxy, sec-butoxy, t-butoxy, n-hexyloxy and the like.

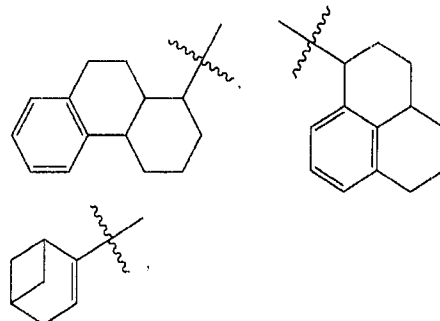
As used herein, unless otherwise noted, "aryl" shall refer to unsubstituted carbocyclic aromatic groups such as phenyl, naphthyl, and the like.

As used herein, unless otherwise noted, " arC_{1-4} alkyl" shall mean any lower alkyl group (i.e. C_{1-4} alkyl group) substituted with an aryl group such as phenyl, naphthyl and the like. Suitable examples of an arC_{1-4} alkyl group include, benzyl, 2-phenylethyl (i.e. Phenyl- CH_2-CH_2-), 3-phenyl-n-propyl (i.e. Phenyl- $CH_2-CH_2-CH_2-$), naphthyl-methyl, and the like.

As used herein, unless otherwise noted, the term "acyl" shall mean a radical formed from an organic acid by removal of the hydroxy group. Suitable example include acetyl, benzoyl, and the like.

As used herein, unless otherwise noted, the term "cycloalkyl" shall mean any stable three to fourteen membered monocyclic, bicyclic, tricyclic or bridged carbon based, saturated ring system, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantanyl, bicyclo[3.1.1]heptyl, and the like.

As used herein, unless otherwise noted, the term "carbocyclyl" shall mean four to fourteen membered, preferably five to thirteen membered, more preferably five to ten membered monocyclic, bicyclic or tricyclic, carbon based ring structure. Similarly, unless otherwise noted, the term "partially unsaturated carbocyclyl" shall mean any five to fourteen, preferably five to thirteen, more preferably five to ten, membered monocyclic, bicyclic or tricyclic, carbon based ring structure containing at least one unsaturated (double or triple) bond. Suitable examples of partially unsaturated carbocyclyl groups include 1,2,3,4-tetrahydronaphthyl, cyclohexen-1-yl, 1-acenaphthenyl,



and the like.

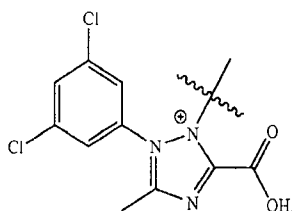
As used herein, unless otherwise noted, "heteroaryl" shall denote any five to seven, preferably five to six, membered monocyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected from the group consisting of O, N and S; or a nine to ten membered bicyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The heteroaryl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure.

US 7,081,463 B2

29

Examples of suitable heteroaryl groups include, but are not limited to, pyrrolyl, furyl, thienyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyran-yl, furazanyl, indolizynyl, indolyl, isoindolynyl, indazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolizynyl, quinolynyl, isoquinolynyl, isothiazolyl, cinnolynyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyrindinyl, pteridinyl, and the like. Preferred heteroaryl groups include thienyl, pyridyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indolyl and quinolynyl.

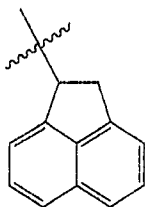
One skilled in the art will recognize that wherein the heteroaryl group contains one or more nitrogen atoms, said heteroaryl group may optionally be present as or within a substituent group in a quaternary form, for example as in 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl), a substituent of the formula



As used herein, the term "heterocycloalkyl" shall denote any five to seven, preferably five to six, membered monocyclic, saturated or partially unsaturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected from the group consisting of O, N and S; or a nine to ten membered saturated, partially unsaturated or partially aromatic bicyclic ring system containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure.

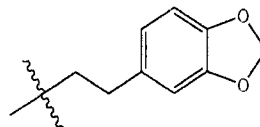
Examples of suitable heterocycloalkyl groups include, but are not limited to, pyrrolinyl, pyrrolidinyl, dioxalanyl, imidazolynyl, imidazolidinyl, pyrazolynyl, pyrazolidinyl, piperidinyl, dioxanyl, morpholynyl, dithianyl, thiomorpholynyl, piperazinyl, trithianyl, indolynyl, chromenyl, 3,4-methylenedioxyphe-nyl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydroisoquinolynyl, 1,2,3,4-tetrahydroquinolynyl, 4,5,6,7-tetrahydrobenzo[b]thienyl and the like. Preferred heterocycloalkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, morpholynyl, 1,2,3,4-tetrahydroisoquinolynyl, 4,5,6,7-tetrahydrobenzo[b]thienyl, 3,4-methylenedioxyphe-nyl and 3,4-dihydro-2H-benzo[b][1,4]dioxepine.

As used herein, the name "1-acenaphthenyl" shall mean a substituent group of the formula

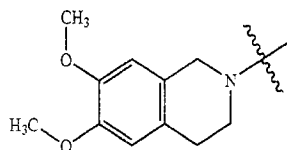


As used herein, the name "2-(3,4-methylenedioxyphe-nyl) ethyl" shall mean a substituent group of the formula

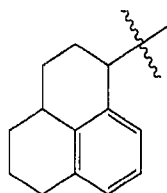
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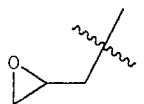
As used herein, the name "2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolynyl)" shall mean a substituent group of the formula



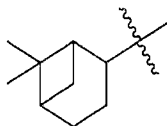
As used herein, the name "2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl" shall mean a substituent group of the formula



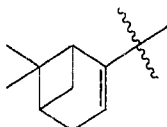
As used herein, the name "oxarinyl-methyl" shall mean a substituent group of the formula



As used herein, the name "6,6-dimethyl-bicyclo[3.1.1]hept-2-enyl" shall mean a substituent group of the formula



As used herein, the name "6,6-dimethyl-bicyclo[3.1.1]hept-2-enyl" shall mean a substituent group of the formula



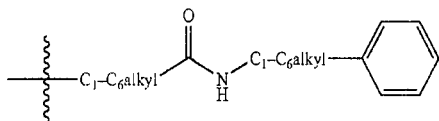
As used herein, the notation "*" shall denote the presence of a stereogenic center.

When a particular group is "substituted" (e.g., alkyl, aryl, carbocyclyl, heterocycloalkyl, heteroaryl), that group may

have one or more substituents, preferably from one to five substituents, more preferably from one to three substituents, most preferably from one to two substituents, independently selected from the list of substituents.

With reference to substituents, the term "independently" means that when more than one of such substituents is possible, such substituents may be the same or different from each other.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC₁-C₆alkylaminocarbonylC₁-C₆alkyl" substituent refers to a group of the formula



Abbreviations used in the specification, particularly the Schemes and Examples, are as follows:

AcCN	Acetonitrile
BiNAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	t-Butoxycarbonyl
CBz	benzyloxycarbonyl (C ₆ H ₅ -CH ₂ -O-C(O)-)
DAMGO	Tyr-D-Ala-Gly-N-methyl-Phe-Gly-ol
DCC	N,N-dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DIPEA or DIEA	Diisopropylethylamine
DMF	N,N-Dimethylformamide
DME	1,2-dimethoxyethane
DMSO	Dimethylsulfoxide
DPDPE	Tyr-D-Pen-Gly-p-Chloro-Phe-D-Pen[Disulfide Bridge: 2-5]
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	Ethylenediaminetetraacetic acid
EGTA	Ethylene glycol-O,O'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid
EtOAc	Ethyl acetate
Fmoc	9-Fluorenylmethoxycarbonyl
HBTU	O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
hex	Hexane
HPLC	High Pressure Liquid Chromatography
KO-t-Bu	Potassium t-butoxide
LiHMDS	Lithium bis(trimethylsilyl)amide
mCPBA	meta-chloroperoxybenzoic acid
MeCN	Acetonitrile
Ms	mesyl or methanesulfonyl group
μW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide
Na ₂ BuO or tBuONa	Sodium t-butoxide
NMP	N-methyl-2-pyrrolidinone
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone) dipalladium (0)
Pd(OAc) ₂	Palladium (II) acetate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
PdCl ₂ (PPh ₃) ₂ or Pd(PPh ₃) ₂ Cl ₂	di(chloro)di(triphenylphosphine)palladium(0)
P(tBu) ₃	Tri-t-butyl phosphine
PEI	Polyethylimine
TEA or Et ₃ N	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TNE Buffer	50 mM Tris-HCl, pH 7.4 + 5 mM EDTA + 150 mM NaCl

-continued

Tris HCl	Tris[hydroxymethyl]aminomethyl hydrochloride
Ts	Tosyl or p-toluenesulfonyl group
U69593	(+)-(5α,7α,8β)-N-methyl-N-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl benzene acetamide

As used herein, unless otherwise noted, the term "eating disorders" shall mean any disorder associated with eating. Suitable examples include, but are not limited to anorexia nervosa, bulimia, binge eating, food cravings, and the like.

As used herein, unless otherwise noted, the term "adrenal disorders" shall mean disorders mediated by the adrenal gland. Suitable examples include, but are not limited to Cushing's syndrome, Addison's disease, and the like.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who is or has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following:

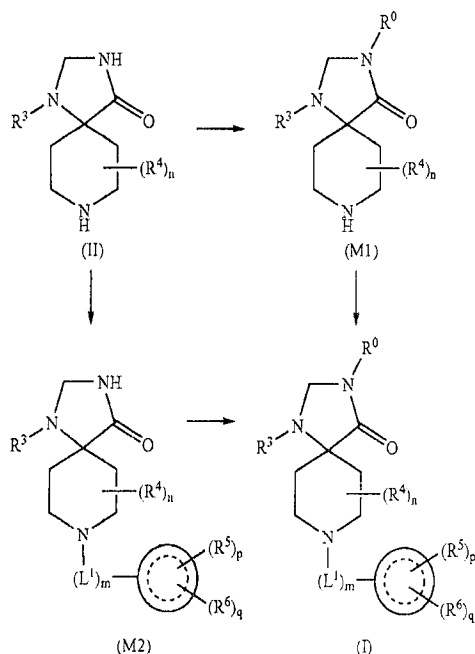
acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, tosylate, triethiodide and valerate.

The compounds of formula (I) of the present invention may be prepared according to the processes described in more detail herein. More particularly, the compounds of

33

formula (I) may be prepared through intermediates of formula (M1) or (M2), as outlined in Scheme 1.

Scheme 1

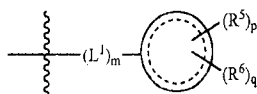


More particularly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted to yield the compound of formula (M1), which is then further reacted to yield the corresponding compound of formula (I).

Alternatively, the compound of formula (II) is reacted to yield the corresponding compound of formula (M2), which is further reacted to yield the corresponding compound of formula (I).

One skilled in the art will recognize that in the processes outlined above, more particularly in the reaction of a compound of formula (II) to form the compound of formula (M1), the N atom at the 8 position of the 1,3,8-triazaspiro[4.5]decan-4-one core is preferably protected, by known methods, with a known protecting group such as BOC, Fmoc, CBz, benzoyl, benzhydryl, and the like. One skilled in the art will further recognize that when a protecting group is utilized in the preparation of the compound of formula (M1), the protecting group is removed, by known methods, prior to reacting the compound of formula (M1) to yield the compound of formula (I).

One skilled in the art will recognize that the processes hereinafter outlined in Schemes 2 to 7 incorporate the R^0 or "top" substituent portion of the molecule onto the core structure, whereas Schemes 8 to 14 incorporate the

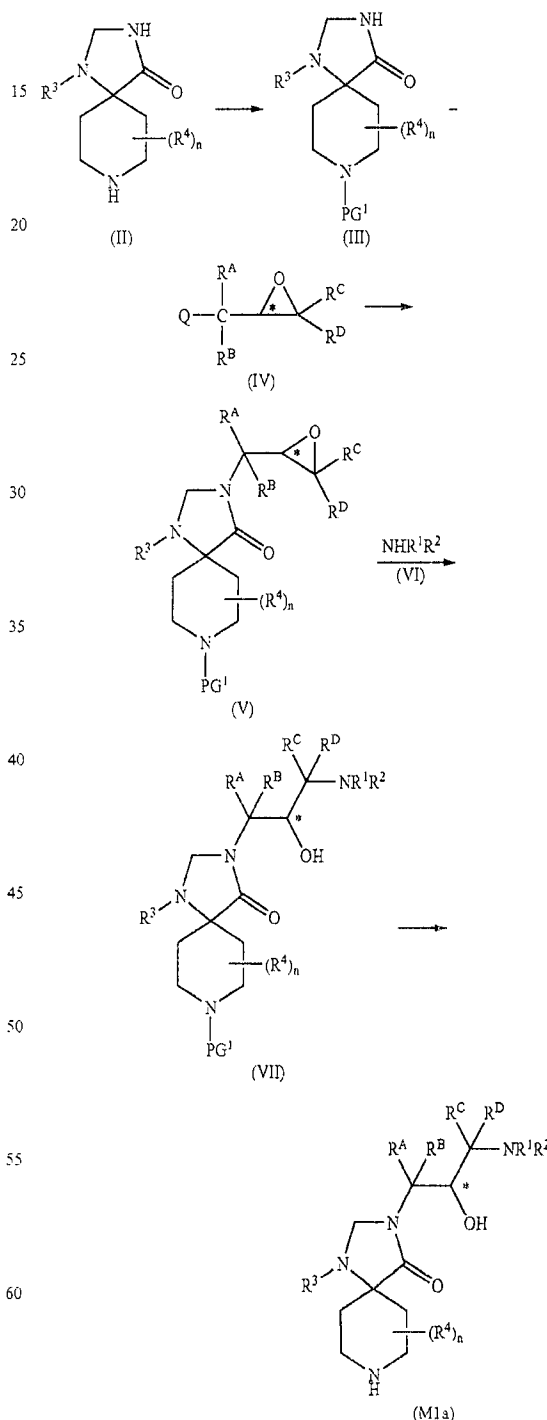


34

that the top and bottom substituent portions may be incorporated into the compound of formula (I) in any order which yields the desired product.

Compounds of formula (M1) wherein R^0 is $-\text{CR}^A\text{R}^B-\text{CH}(\text{OH})-\text{CR}^C\text{R}^D-\text{X}$ and X is NR^1R^2 may be prepared from a suitably substituted compound of formula (II) according to the process outlined in Scheme 2.

Scheme 2



or "bottom" substituent portion of the molecule onto the core structure. One skilled in the art will further recognize

35

Accordingly, a suitably substituted compound of formula (II), is protected by known methods, with a suitably protecting group PG¹, such as t-butoxycarbonyl (BOC), CBz, Fmoc, benzhydryl, triphenylmethyl, 4-methoxybenzyl, benzoyl, and the like, to yield the corresponding compound of formula (III).

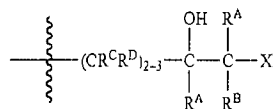
The compound of formula (III) is reacted with a suitable substituted compound of formula (IV) wherein Q is a suitable leaving group such as Cl, Br, I, tosylate, mesylate, and the like, a known compound or compound prepared by known methods, in the presence of a base such as NaH, KO-t-Bu, K₂CO₃, NaHMDS, LiHMDS, and the like, in an organic solvent such as NMP, DMF, THF, and the like, to yield the corresponding compound of formula (V).

The compound of formula (V) is reacted with a suitably substituted amine of formula (VI), a known compound or compound prepared by known methods, in an organic solvent such as ethanol, acetonitrile, methanol, isopropanol, and the like, to yield the corresponding compound of formula (VII).

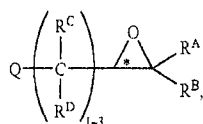
The compound of formula (VII) is de-protected by known methods, to yield the corresponding compound of formula (M1a).

One skilled in the art will recognize that in the preparation of compounds of formula (I) and (M1a) as in Scheme 2 above (i.e. in reactions where the oxarinyl group is opened with a suitably substituted compound of formula (VI)), the stereo-configuration of the hydroxy group will be determined by the stereo-configuration of the compound of formula (IV), with the naming (R or S) of the stereo-center based on chemical nomenclature rules. Thus, for example, wherein the process outlined in Scheme 2 above R¹, R², R⁴, R^B, R^C and R^D are each hydrogen, the compound of formula (IV) is 2-(R)-chloromethyl-oxirane, then the compound of formula (M1a) will have the hydroxy group in the (R) position.

Compounds of formula (M1a) wherein R⁰ is



may be similarly prepared according to the process outlined in Scheme 2 above, with substitution of a suitably substituted compound of formula (VII)

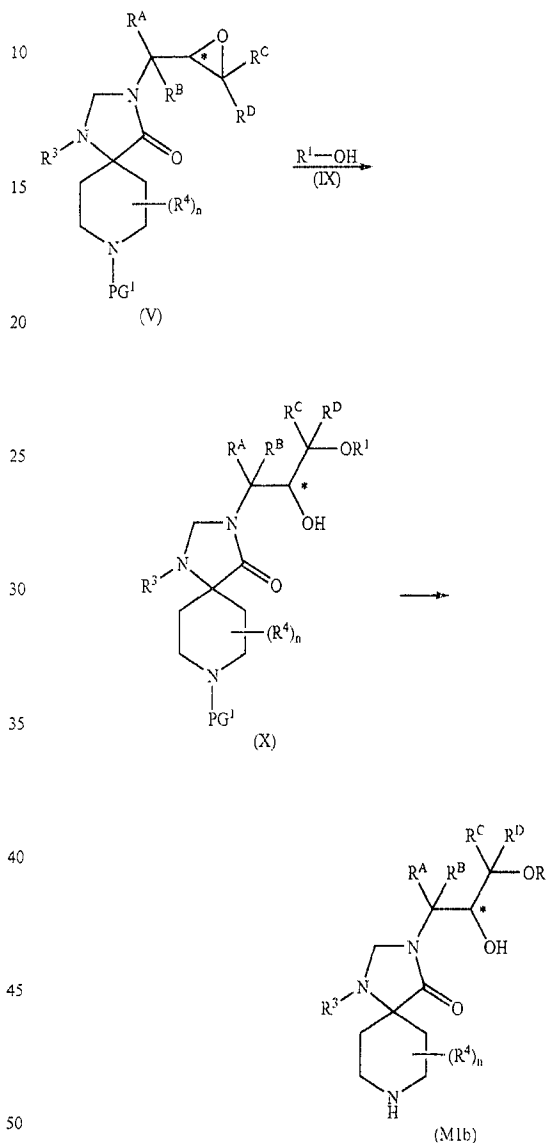


wherein Q is a suitable leaving group as previously defined, a known compound or compound prepared by known methods, for the compound (IV).

36

Compounds of formula (M1) wherein X is —O—R¹ may be prepared from a suitably substituted compound of formula (V) according to the process outlined in Scheme 3.

Scheme 3



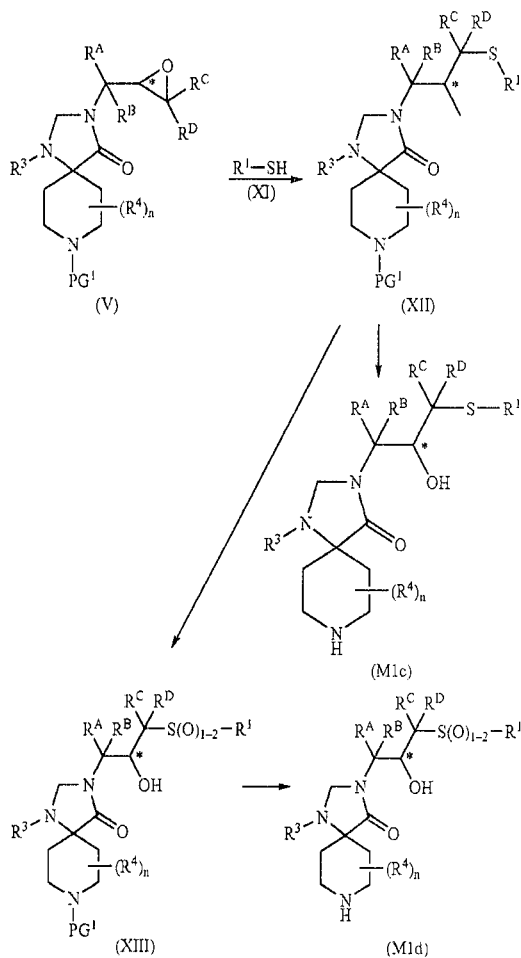
Accordingly, a suitably substituted compound of formula (V), is reacted with suitably substituted compound of formula (IX), a known compound or compound prepared by known methods, in the presence of a base such as NaH, KH, sodium trimethylsilylamide, TEA, DIPEA, and the like, wherein the base is present in amount equal to or greater than about one molar equivalent, in an organic solvent such as THF, NMP, DMF, and the like, to yield the corresponding compound of formula (X).

The compound of formula (X) is de-protected, by known methods, to yield the corresponding compound of formula (M1b).

37

Compounds of formula (M1) wherein X is selected from the group consisting of $-\text{S}-\text{R}^1$, $-\text{SO}-\text{R}^1$ or $-\text{SO}_2-\text{R}^1$ may be prepared from a suitably substituted compound of formula (V) according to the process outlined in Scheme 4.

Scheme 4



Accordingly, a suitably substituted compound of formula (V) is reacted with a suitably substituted compound of formula (XI), a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, and the like, in a protic solvent such as ethanol, methanol, NMP, and the like, or a mixture thereof, preferably at an elevated temperature in the range of about room temperature to about 100°C ., preferably at a temperature of about 50 to about 100°C ., to yield the corresponding compound of formula (XII).

The compound of formula (XII) is de-protected by known methods, to yield the corresponding compound of formula (M1c), wherein X is $-\text{S}-\text{R}^1$.

Alternatively, the compound of formula (XII) is oxidized with an oxidizing agent such as hydrogen peroxide, mCPBA, and the like, according to known methods, to yield the corresponding compound of formula (XIII).

The compound of formula (XIII) is de-protected by known methods, to yield the corresponding compound of formula (M1d), wherein X is $-\text{SO}-\text{R}^1$ or $-\text{SO}_2-\text{R}^1$.

One skilled in the art will recognize that in the processes described in Scheme 4 above, the PG^1 protecting group on

38

the N atom at the 8-position of the 1,3,8-triazaspiro[4.5]decan-4-one is not mandatory (but may be preferred), as the reactions will yield the desired compounds even in the absence of protection of the N atom.

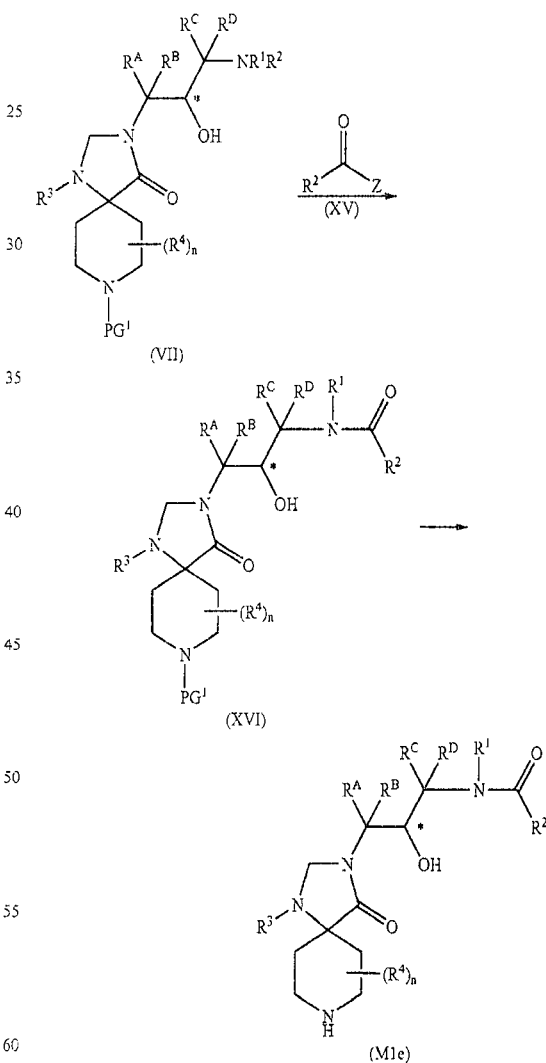
One skilled in the art will recognize that compounds of formula (M1) wherein X is selected from $-\text{S}-(\text{alkyl})-\text{NR}^1\text{R}^2$, $-\text{SO}-(\text{alkyl})-\text{NR}^1\text{R}^2$ or $-\text{SO}_2-(\text{alkyl})-\text{NR}^1\text{R}^2$ may be similarly prepared according to the process outlined in Scheme 4 above, with substitution of a suitably substituted compound of formula (XIV)



a known compound or compound prepared by known methods, for the compound of formula (XI).

Compounds of formula (M1) wherein X is $-\text{NR}^1-\text{C}(\text{O})-\text{R}^2$ may be prepared according to the process outlined in Scheme 5.

Scheme 5



Accordingly, a suitably substituted compound of formula (VII), wherein R^1 is hydrogen, is reacted with a suitably substituted compound of formula (XV), wherein Z is Cl, Br or OH, a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA,

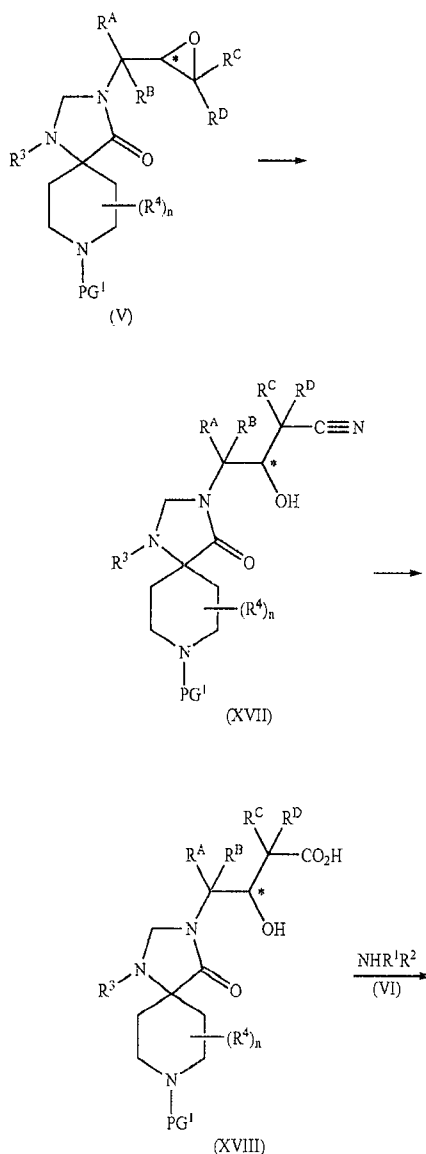
39

pyridine, and the like, wherein the base is present in an amount equal to or greater than about one molar equivalent, in an organic solvent such as THF, DMF, NMP, DCM, and the like, preferably at room temperature, to yield the corresponding compound of formula (XVI). Wherein the compound of formula (XV) Z is OH, the compound of formula (VII) is reacted with the compound of formula (XV) in the presence of a coupling agent such as HBTU, DCC, and the like.

The compound of formula (XVI) is de-protected by known methods, to yield the corresponding compound of formula (M1e).

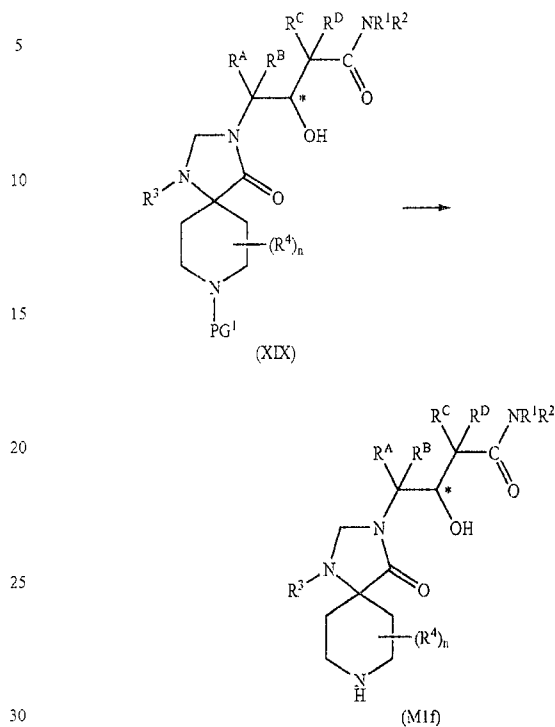
Compounds of formula (M1) wherein X is $\text{---C(O)---NR}^1\text{NR}^2$ may be prepared according to the process outlined in Scheme 6.

Scheme 6



40

-continued



Accordingly, a suitably substituted compound of formula (V) is reacted with potassium cyanide, in a co-solvent such as methanol-water, and the like, preferably at room temperature, to yield the corresponding compound of formula (XVII).

The compound of formula (XVII) is reacted with a base such as KOH, NaOH, and the like or with an acid such as H_2SO_4 , HCl, and the like, or NaBH_4 in the presence of AlCl_3 , to yield the corresponding compound of formula (XVIII).

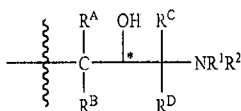
The compound of formula (XVIII) is reacted with a suitably substituted compound of formula (VI), a known compound or compound prepared by known methods, in the presence of a coupling agent such as DCC, EDCI, and the like, in an organic solvent such as CH_2Cl_2 , THF, DMF, and the like, to yield the corresponding compound of formula (XIX).

The compound of formula (XIX) is de-protected by known methods, to yield the corresponding compound of formula (M1f).

Alternatively, the compound of formula (XVII) is reacted with a suitably substituted alcohol, a compound of the formula $\text{R}^1\text{---OH}$, a known compound or compound prepared by known methods, in the presence of an acid such as acetic acid, H_2SO_4 , HCl, and the like, to yield the corresponding compound of formula (M1) wherein X is C(O)NHR^1 . One skilled in the art will recognize that compounds of formula (M1) wherein X is $\text{C(O)N(R}^1)_2$ may be similarly prepared by reacting the compound of formula (XVII) with a suitably substituted alcohol of the formula $\text{R}^1\text{---OH}$, in the presence of an acid such as H_2SO_4 , HCl, and the like, wherein the alcohol of formula $\text{R}^1\text{---OH}$ is present in an excess amount.

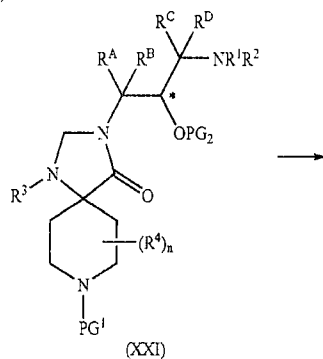
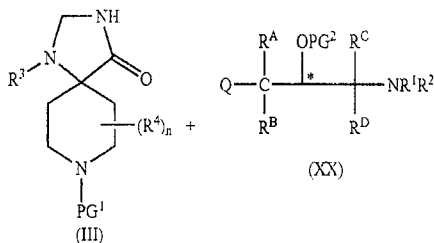
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Compounds of formula (M1a) wherein R^0 is



may alternatively be prepared according to the process outlined in Scheme 7.

Scheme 7



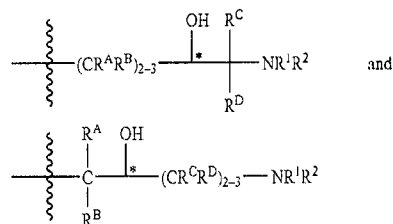
(M1a)

Accordingly, a suitably substituted compound of formula (III), is reacted with a suitably substituted compound of formula (XX), wherein Q is a suitable leaving group such as Cl, Br, I, tosylate, mesylate, and the like, and wherein PG² is a suitably protecting group such as benzyl, acyl, and the like, a known compound or compound prepared by known methods, in the presence of a base such as NaH, KO-t-Bu, K₂CO₃, NaHMDS, LiHMDS, and the like, in an organic solvent such as NMP, DMF, THF, and the like, to yield the corresponding compound of formula (XXI).

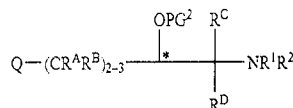
The compound of formula (XXI) is de-protected by known methods, to yield the corresponding compound of formula (M1a). One skilled in the art will recognize that the protecting groups PG¹ and PG² on the compound of formula (XXI) may be removed simultaneously or sequentially, in any order, by known methods.

42

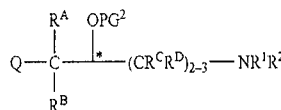
One skilled in the art will recognize, that compounds of formula (M1) wherein R^0 is selected from the group consisting of



may be similarly prepared according to the process outlined in Scheme 7 above, with selection and substitution of a suitably substituted compound of formula (XXII)



or the compound of formula (XXIII),



respectively, for the compound of formula (XX).

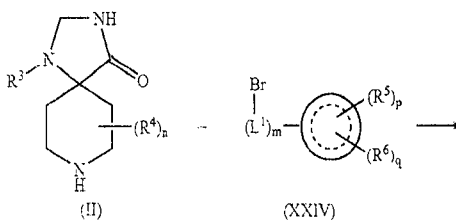
One skilled in the art will recognize that the processes outlined in Schemes 2 to 7 above may be similarly applied to the preparation of compounds of formula (I) with substitution of a suitably substituted compound of formula (M2) for the compound of formula (II).

Compounds of formula (M2), wherein m is an integer from 0 to 1, provided that when



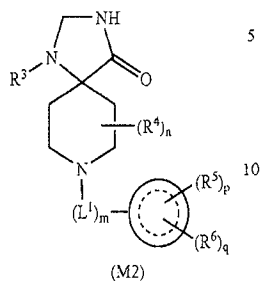
is aryl or heteroaryl, then m is 1, may be prepared according to the process outlined in Scheme 8.

Scheme 8



43

-continued



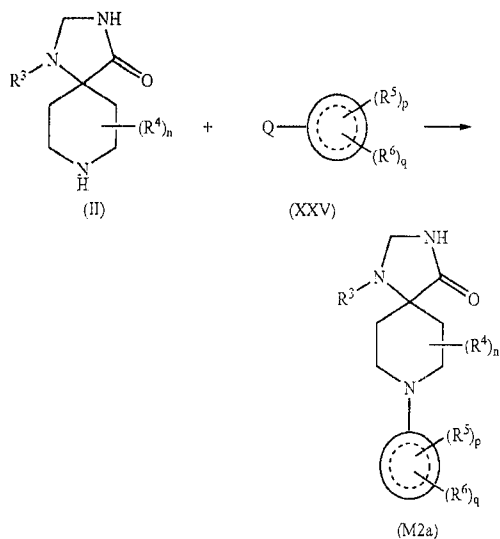
Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXIV), a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, pyridine, Na_2CO_3 , K_2CO_3 , and the like, wherein the base is present in an amount equal to or greater than about one molar equivalent, in an organic solvent such as DMF, DMSO, NMP, and the like, to yield the corresponding compound of formula (M2).

Compounds of formula (M2) wherein m is 0 and



is aryl or heteroaryl may be prepared according to the process outlined in Scheme 9.

Scheme 9



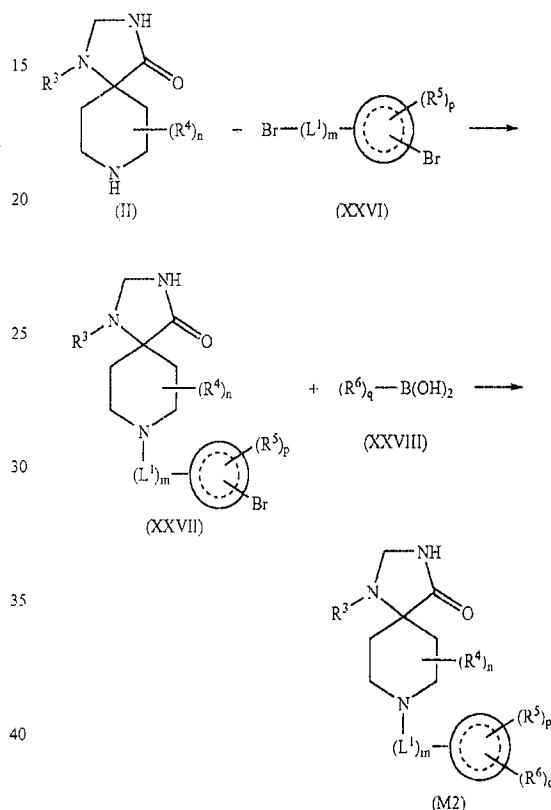
Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXV), wherein Q is a suitable leaving group such as Cl, Br, I, triflate, and the like, a known compound or compound prepared by known methods, in the presence of

44

a catalyst such as $\text{Pd}(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3$, and the like, in the presence of a phosphine ligand such as BINAP, $\text{P}(\text{tBu})_3$, and the like, in the presence of a base such as Na_2CO_3 , tBuONa , and the like, in an organic solvent such as toluene, dioxane, and the like, preferably at an elevated temperature in the range of about 30 to about 120° C., to yield the corresponding compound of formula (M2a).

Compounds of formula (M2) may alternatively be prepared according to the process outlined in Scheme 10.

Scheme 10



Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXVI), a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, pyridine, Na_2CO_3 , K_2CO_3 , and the like, wherein the base is present in an amount equal to or greater than about one molar equivalent, in an organic solvent such as DMF, DMSO, NMP, and the like, to yield the corresponding compound of formula (XXVII).

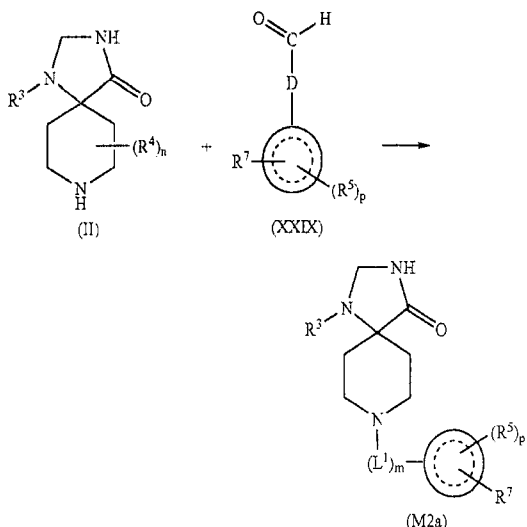
The compound of formula (XXVII) is reacted with a suitably substituted boronic acid, a compound of formula (XXVIII), a known compound or compound prepared by known methods, in the presence of a catalyst such as $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and the like, in the presence of a base such as Na_2CO_3 , K_3PO_4 , and the like, in a non-protic organic solvent or mixture thereof, such as toluene, DME, DMF, and the like, or a mixture thereof such as toluene/ethanol, and the like, to yield the corresponding compound of formula (M2).

One skilled in the art will recognize that for compounds of formula (XXVI), the Br may alternatively be replaced with an I or triflate.

45

Compounds of formula (M2) wherein m is 1, L^1 is C_{1-6} alkyl or C_{3-6} alkenyl, R^6 is $(L^2)_0-R^7$ and R^7 is an aryl or heteroaryl group may be prepared according to the process outlined in Scheme 11.

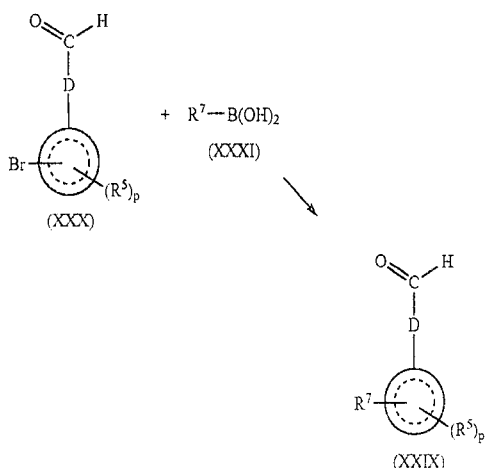
Scheme 11



Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted aldehyde, a compound of formula (XXIX), wherein D is C_{1-5} alkyl or C_{2-5} alkenyl, a known compound or compound prepared by known methods, in the presence of a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride, and the like, in the presence of an acid such as acetic acid, and the like, in an organic solvent such as DCE, THF, acetonitrile, and the like, to yield the corresponding compound of formula (M2a).

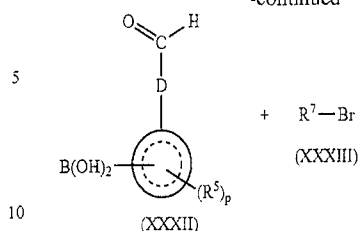
Compounds of formula (XXIX) may be prepared according to the processes outlined in Scheme 12.

Scheme 12



46

-continued



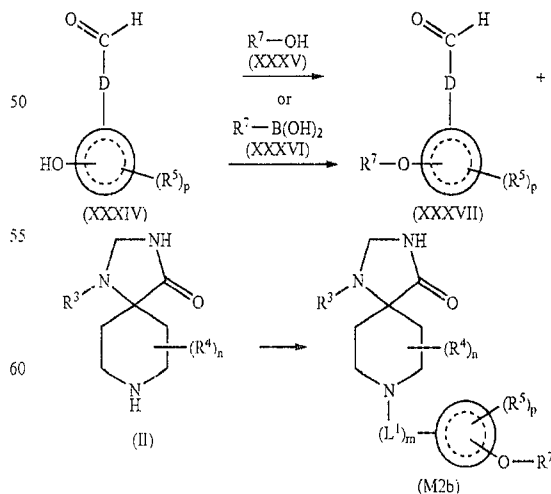
Accordingly, a suitably substituted compound of formula (XXX), wherein D is C_{1-5} alkyl or C_{2-5} alkenyl, a known compound or compound prepared by known methods, is reacted with a suitably substituted boronic acid, a compound of formula (XXXI), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and the like, in the presence of a base such as Na_2CO_3 , $NaHCO_3$, K_3PO_4 , and the like, in a non-protic organic solvent or mixture thereof such as toluene, toluene/ethanol, DME, DMF, benzene, and the like, to yield the corresponding compound of formula (XXIX).

Alternatively, a suitably substituted compound of formula (XXXII), wherein D is C_{1-5} alkyl or C_{2-5} alkenyl, a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXXIII), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and the like, in the presence of a base such as aqueous $NaHCO_3$, Na_2CO_3 , K_3PO_4 , and the like, in an organic solvent such as DME, DMF, toluene, benzene, and the like, to yield the corresponding compound of formula (XXIX).

One skilled in the art will recognize that for compounds of formula (XXXI) and/or compounds of formula (XXXIII), the Br may alternatively be replaced with an I or triflate.

Compounds of formula (M2) wherein q is 1, R^6 is $(L^2)_1-R^7$ and L^2 is $-O-$ may be prepared according to the process outlined in Scheme 13.

Scheme 13



47

Accordingly, a suitably substituted compound of formula (XXXIV), wherein D is C_{1-5} alkyl or C_{2-5} alkenyl, a known compound or compound prepared by known methods, is reacted with a suitably substituted alcohol, a compound of formula (XXXV), a known compound or compound prepared by known methods, in the presence of an activating agent such as tributylphosphine, triphenylphosphine, diphenyl-2-pyridylphosphine, and the like, in an anhydrous organic solvent such as benzene, THF, DCM, and the like, (via a Mitsunobu reaction) in the presence of a dehydrating agent such as 1,1'-(azodicarbonyl)dipiperidine, diethylazodicarboxylate, diisopropylazodicarboxylate, and the like, to yield the corresponding compound of formula (XXXVII).

Alternatively, the compound of formula (XXXVII) may be prepared by reacting a compound of formula (XXXIV) with a compound of formula (XXXV), wherein the hydroxy (OH) group on the compound of formula (XXXV) is replaced with a fluoro, bromo or triflate, in the presence of a base such as K_2CO_3 , sodium carbonate, sodium bicarbonate, and the like, in a dipolar aprotic solvent such as $(CH_3)_2NCOCH_3$, DMF, DMSO, and the like.

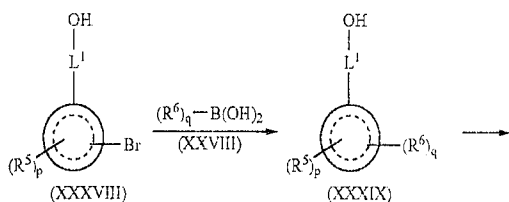
Alternatively, the compound of formula (XXXIV) is reacted with a suitably substituted boronic acid, a compound of formula (XXXVI), a known compound or compound prepared by known methods, in the presence of a catalyst such as copper (II) acetate, and the like, in the presence of an base such as TEA, pyridine, and the like, in the presence of molecular sieves, preferably 4 Angstrom molecular sieves, in an organic solvent such as DCM, DCE, and the like, preferably at ambient temperature, to yield the corresponding compound of formula (XXXVII).

The compound of formula (XXXVII) is reacted with a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, in the presence of a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride, and the like, in an organic solvent such as DCE, THF, acetonitrile, and the like, to yield the corresponding compound of formula (M2b).

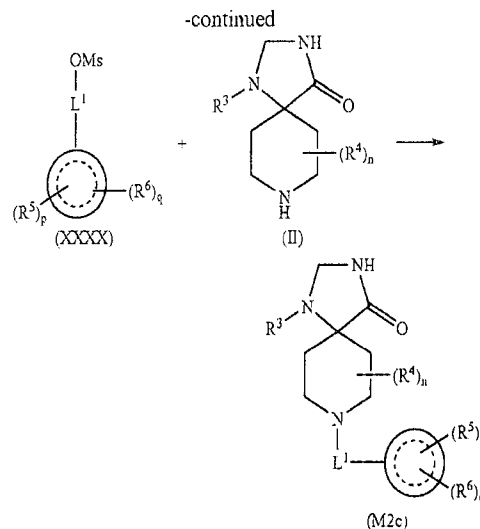
One skilled in the art will recognize that compounds of formula (M2) wherein L^2 is $-S-$ may similarly be prepared according to the process outlined above with appropriate selection and substitution of suitably substituted starting materials (e.g. substitution of the OH group on the compound of formula (XXXIV) with Cl or Br and substitution of a suitably substituted compound of the formula R^7-SH for the compound of formula (XXXV), preferably in the presence of a copper catalyst, according to known methods. The sulfur group may then be further oxidized with a suitable oxidizing agent such as hydrogen peroxide, mCPBA, and the like, according to known methods, to yield the corresponding compound wherein L^2 is selected from $-SO-$ or $-SO_2-$.

Compounds of formula (M2) wherein R^6 is $-L^2-R^7$ and L^2 is C_{2-4} alkenyl may be prepared according to the process outlined in Scheme 14.

Scheme 14



48



Accordingly, a suitably substituted compound of formula (XXXVIII), a known compound or compound prepared by known methods, is reacted with a suitably substituted boronic acid, a compound of formula (XXXVI), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and the like, in the presence of a base such as $NaHCO_3$, K_2CO_3 , Na_2CO_3 , and the like, to yield the corresponding compound of formula (XXXIX).

The compound of formula (XXXIX) is reacted with methanesulfonyl chloride, a known compound, in the presence of an organic base such as TEA, DIPEA, N-methylmorpholine, and the like, in an aprotic solvent such as DCM, THF, acetonitrile, $CHCl_3$, and the like, to yield the corresponding compound of formula (XXXX), wherein Ms is a mesyl group.

The compound of formula (XXXX) is reacted with a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, in the presence of a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride, and the like, in an organic solvent such as DCM, DCE, THF, methanol, acetonitrile, and the like, to yield the corresponding compound of formula (M2c).

One skilled in the art will recognize that the processes outlined in Schemes 8 to 14 above may be similarly applied to the preparation of compounds of formula (I) with substitution of a suitably substituted compound of formula (M1) for the compound of formula (II).

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoi-

somers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (–)-di-p-toluoyl-D-tartaric acid and/or (+)-di-p-toluoyl-L-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which

are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term “administering” shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Following the procedures described herein, representative compounds of the present invention were prepared as listed in Tables 1–8. In the Tables below, the column headed with a * shall define the stereochemical configuration of the bond denoted with the “*” symbol in the general structure at the head of the table. In addition to “R” and “S” designations, racemic mixtures will be denoted with the term “Rac”. For the



substituent, the stereoconfiguration is racemic, unless otherwise noted with an “R” or “S”. In the columns headed $(L^1)_m$, a listing of “absent” shall mean that m is 0.

TABLE 1

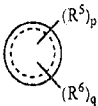
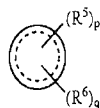
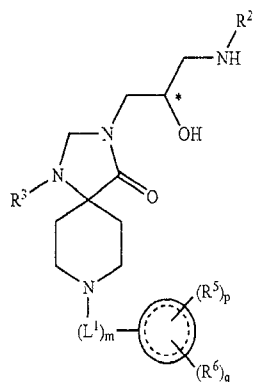
ID #	*	R ²	R ³	(L ¹) _m	
1	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH ₂	cyclooctyl
2	R	3,4-dimethoxy benzyl	4-fluorophenyl	CH ₂	cyclooctyl
3	R	3,5-di(trifluoromethyl)benzyl	4-fluorophenyl	CH ₂	cyclooctyl
4	R	2-(4-imidazolyl)ethyl	4-fluorophenyl	CH ₂	cyclooctyl
5	R	4-bromobenzyl	4-fluorophenyl	CH ₂	cyclooctyl
6	R	3,4-dimethoxy benzyl	4-fluorophenyl	CH ₂	cyclooctyl
7	S	2,4-difluorobenzyl	4-fluorophenyl	CH ₂	cyclooctyl
8	S	2,4-dimethoxy benzyl	4-fluorophenyl	CH ₂	cyclooctyl
9	S	4-biphenyl	4-fluorophenyl	CH ₂	cyclooctyl
10	S	2-ethoxybenzyl	4-fluorophenyl	CH ₂	cyclooctyl
11	S	2-phenylethyl	4-fluorophenyl	CH ₂	cyclooctyl
12	S	2,5-difluorobenzyl	4-fluorophenyl	CH ₂	cyclooctyl
13	S	2-(5-bromopyridyl)	4-fluorophenyl	CH ₂	cyclooctyl
14	S	2-methoxybenzyl	4-fluorophenyl	CH ₂	cyclooctyl
15	S	4-bromobenzyl	4-fluorophenyl	CH ₂	cyclooctyl
16	S	3,5-di(trifluoromethyl)benzyl	4-fluorophenyl	CH ₂	cyclooctyl
17	S	1-adamantanylmethyl	4-fluorophenyl	CH ₂	cyclooctyl
18	S	3-methylbenzyl	4-fluorophenyl	CH ₂	cyclooctyl

TABLE 1-continued



ID #	*	R²	R³	(L¹) _m	(R⁵) _p (R⁶) _q
19	S	2-(2,5-dimethoxy-2,5-dihydro-furyl)-methyl	4-fluorophenyl	CH₂	cyclooctyl
20	S	3-bromobenzyl	4-fluorophenyl	CH₂	cyclooctyl
21	S	3-chlorobenzyl	4-fluorophenyl	CH₂	cyclooctyl
22	S	3,4-dimethoxy benzyl	4-fluorophenyl	CH₂	cyclooctyl
23	S	4-nitrobenzyl	4-fluorophenyl	CH₂	cyclooctyl
24	S	4-pyridyl	4-fluorophenyl	CH₂	cyclooctyl
25	S	3,5-dimethoxy-benzyl	4-fluorophenyl	CH₂	cyclooctyl
26	S	2-(2-thienyl)ethyl	4-fluorophenyl	CH₂	cyclooctyl
27	S	2-methylbenzyl	4-fluorophenyl	CH₂	cyclooctyl
28	S	2-(4-imidazolyl)-ethyl	4-fluorophenyl	CH₂	cyclooctyl
29	S	4-trifluoromethyl benzyl	4-fluorophenyl	CH₂	cyclooctyl
30	S	2-(4-bromophenyl) ethyl	4-fluorophenyl	CH₂	cyclooctyl
31	S	2,4-dichlorobenzyl	4-fluorophenyl	CH₂	cyclooctyl
32	S	3-pyridylmethyl	4-fluorophenyl	CH₂	cyclooctyl
33	S	3-trifluoromethyl benzyl	4-fluorophenyl	CH₂	cyclooctyl
34	S	2-(4-methoxy-phenyl)ethyl	4-fluorophenyl	CH₂	cyclooctyl
35	S	3-methoxybenzyl	4-fluorophenyl	CH₂	cyclooctyl
36	S	4-pyridyl	4-fluorophenyl	CH₂	cyclooctyl
38	S	2-(3,4-dimethoxy phenyl)ethyl	4-fluorophenyl	CH₂	cyclooctyl
39	S	2-pyridylmethyl	4-fluorophenyl	CH₂	cyclooctyl
40	S	1-naphthyl	4-fluorophenyl	CH₂	cyclooctyl
41	S	4-methylbenzyl	4-fluorophenyl	CH₂	cyclooctyl
42	S	2-(3,5-dimethyl-pyridyl)	4-fluorophenyl	CH₂	cyclooctyl
43	S	3,4,5-trimethoxy-benzyl	4-fluorophenyl	CH₂	cyclooctyl
44	S	2-bromobenzyl	4-fluorophenyl	CH₂	cyclooctyl
45	S	2,3-dimethoxy benzyl	4-fluorophenyl	CH₂	cyclooctyl
46	S	3,4-dichlorobenzyl	4-fluorophenyl	CH₂	cyclooctyl
47	R	2-(4-morpholinyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
48	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
49	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
50	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH₂CH₂	phenyl
51	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH₂CH₂	phenyl
52	Rac	2-(3,4-dimethoxy-phenyl)ethyl	phenyl	absent	1-acenaphthenyl
53	R	2-(4-morpholinyl) ethyl	phenyl	absent	1-acenaphthenyl
251	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH₂	1-naphthyl
253	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH₂	1-naphthyl
254	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH₂	i-naphthyl
255	S	2-(2-nitro-4,5-dimethoxy-phenyl) ethyl	4-fluorophenyl	CH₂	1-naphthyl
259	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH₂	2-naphthyl
261	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH₂	2-naphthyl
262	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH₂	2-naphthyl
265	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH₂	4-chlorophenyl
267	R	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH₂	4-chlorophenyl
268	R	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH₂	4-chlorophenyl
269	R	2-(2-nitro-4,5-dimethoxy-phenyl) ethyl	4-fluorophenyl	CH₂	4-chlorophenyl
271	R	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	absent	i-acenaphthenyl

TABLE 1-continued

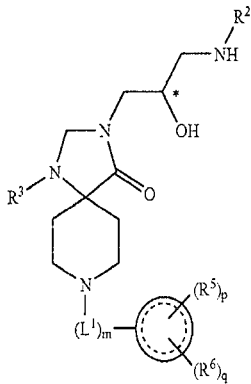
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276	S	2-(2-nitro-4,5-dimethoxy-phenyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
279	S	1-(4-butoxy-carbonyl)-2-phenylethyl	4-fluorophenyl	CH ₂	cyclooctyl
281	S	2-ethoxy-phenyl	4-fluorophenyl	CH ₂	cyclooctyl
282	S	4-((1-phenyl-pyrazol-2-yl)-amino-sulfonyl)phenyl	4-fluorophenyl	CH ₂	cyclooctyl
285	S	4-cyclohexyl-phenyl	4-fluorophenyl	CH ₂	cyclooctyl
292	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	5-phenyl-2-thienyl
293	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH ₂	5-phenyl-2-thienyl
298	R	2-(4-morpholinyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
300	R	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
307	S	3,4-dimethoxy-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
308	S	4-nitrobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
309	S	2-(1,2,3,4-tetrahydro-isoquinoliny)	4-fluorophenyl	absent	1-acenaphthenyl
310	S	4-biphenyl	4-fluorophenyl	absent	1-acenaphthenyl
311	S	2-furylmethyl	4-fluorophenyl	absent	1-acenaphthenyl
312	S	3-iodobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
314	S	3,4-difluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
315	S	3-bromobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
316	S	4-chlorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
317	S	4-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
318	S	2-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
319	S	3,5-di(trifluoromethyl) benzyl	4-fluorophenyl	absent	1-acenaphthenyl
320	S	3,4,5-tri-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
321	S	3-fluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
322	S	3-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
323	S	2-(4-methoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
324	S	3,5-dimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
325	S	4-methyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
326	S	3-(phenyl)-n-propyl	4-fluorophenyl	absent	1-acenaphthenyl
327	S	4-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
328	S	4-trifluoromethoxy benzyl	4-fluorophenyl	absent	1-acenaphthenyl
329	S	2-(phenoxy)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
330	S	2-methyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
331	S	2,3-dimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
338	S	3-di(n-butyl)amino-n-propyl	4-fluorophenyl	absent	1-acenaphthenyl
341	S	2-phenylethyl	4-fluorophenyl	absent	1-acenaphthenyl
342	S	2,5-difluoro-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
343	S	3,4-dichloro-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
344	S	3-trifluoromethyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
345	S	benzyl	4-fluorophenyl	absent	1-acenaphthenyl
346	S	2-fluoro-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
347	S	4-trifluoromethyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
348	S	4-methoxycarbonyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
349	S	2,4-dimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
350	S	3-chlorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
351	S	3-ethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
352	S	4-bromobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
353	S	3-methylbenzyl	4-fluorophenyl	absent	1-acenaphthenyl
354	S	4-fluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
355	S	2-bromobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
356	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
358	S	2,4-difluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl

TABLE 1-continued

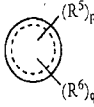
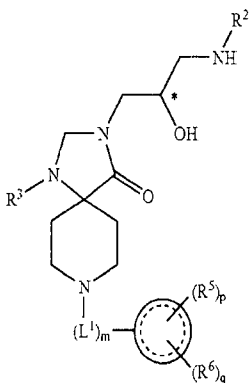
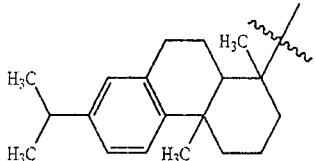
ID #	*	R ²	R ³	(L ¹) _m	
					
365	S	2-(4-bromophenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
366	S	3-pyridyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
367	S	2,4,6-trimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
368	S	2,4-dichlorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
370	S	3-nitrobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
371	S	1-naphthyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
372	S	2-(2-thienyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
373	S	2-trifluoromethyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
385	R	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
386	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
387	R	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
374	S		4-fluorophenyl	absent	1-acenaphthenyl
375	S	2-(4,6-dimethyl)-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
376	S	4-pyridyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
378	R	2-pyridyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
379	R	4-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
380	R	3-(6-methoxy-pyridyl)	4-fluorophenyl	absent	1-acenaphthenyl
381	R	3-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
383	R	2-(5-methyl-pyridyl)	4-fluorophenyl	absent	1-acenaphthenyl
390	R	2-(3,4-methylene dioxypheyl)ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
392	R	4-methoxybenzyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
393	R	4-pyridyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
396	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
398	S	4-methoxybenzyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
418	S	2-(3,4-methylene dioxypheyl)ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
419	S	2-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
420	R	H	4-fluorophenyl	absent	R-1-acenaphthenyl
421	R	2-pyridyl	4-fluorophenyl	absent	R-1-acenaphthenyl
422	S	H	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
424	S	H	4-fluorophenyl	absent	R-1-acenaphthenyl
425	R	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
426	R	H	4-fluorophenyl	absent	S-1-acenaphthenyl
427	R	methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
430	S	H	4-fluorophenyl	absent	S-1-acenaphthenyl
431	S	methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
437	S	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
438	R	H	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
443	S	methoxy	4-fluorophenyl	absent	R-1-acenaphthenyl
444	S	ethoxy	4-fluorophenyl	absent	R-1-acenaphthenyl
446	R	2-(3,4-methylene dioxypheyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
448	S	2-phenoxethyl	4-fluorophenyl	absent	1-acenaphthenyl
451	S	4-(1-phenyl-2-pyrazolyl-amino-sulfonyl)phenyl	4-fluorophenyl	CH ₂	cyclooctyl

TABLE 1-continued

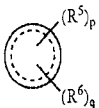
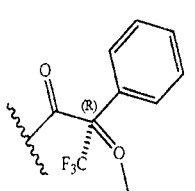
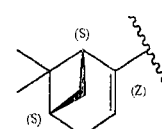
ID #	*	R ²	R ³	(L ¹) _m	
452	S	4-carboxy-benzyl	4-fluorophenyl	CH ₂	cyclooctyl
453	S	H	4-fluorophenyl	CH ₂	cyclooctyl
454	S	n-butyl	4-fluorophenyl	CH ₂	cyclooctyl
458	S	phenyl	4-fluorophenyl	CH ₂	2-trifluoromethyl-6-chloro-phenyl
461	R	2-(2-nitro-4,5-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
463	S	benzyloxy	4-fluorophenyl	absent	R-1-acenaphthenyl
464	R	4-(aminoethyl)-phenyl	4-fluorophenyl	absent	S-1-acenaphthenyl
600	S	phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
601	R	4-(t-butoxycarbonyl-amino-ethyl)-phenyl	4-fluorophenyl	absent	S-1-acenaphthenyl
602	S	4-fluorophenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
603	S	3,4-dimethoxy-phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
604	S	4-(methyl)-phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
605	R	2-(aminoethyl)-phenyl	4-fluorophenyl	absent	S-1-acenaphthenyl
606	S	1-cyclopropyl	4-fluorophenyl	absent	R-1-acenaphthenyl
607	S	1-Adamantanyl	4-fluorophenyl	CH ₂	3,5-bis-trifluoromethyl-phenyl
608	S	4-pyridyl	4-fluorophenyl	CH ₂	3,5-bis-trifluoromethyl-phenyl
609	S	1-(3-pyridyl)-methyl	4-fluorophenyl	CH ₂	3,5-bis-trifluoromethyl-phenyl
610	S	3-di(n-butyl)amino-n-propyl	4-fluorophenyl	CH ₂	3,5-bis-trifluoromethyl-phenyl
611	R	1-(3-pyridyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
612	S	1-(4-pyridyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
613	S	1-(3-pyridyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
614	S	1-(2-thienyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
615	R		4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
616	S	H	4-fluorophenyl	absent	cyclooctyl
617	S	4-pyridinyl	4-fluorophenyl	absent	cyclooctyl
618	S	4-pyridinyl	4-fluorophenyl	CH ₂	

TABLE 1-continued

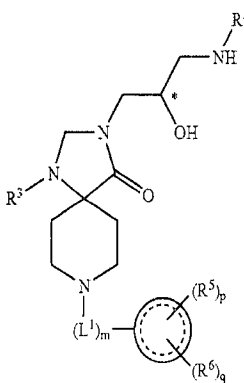
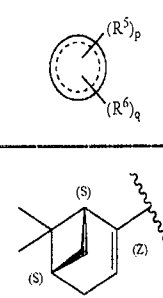
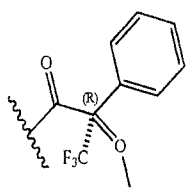
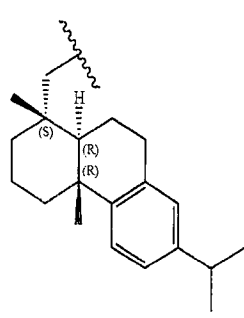
ID #	*	R ²	R ³	(L ¹) _m	
619	S	H	4-fluorophenyl	CH ₂	
620	R	H	4-fluorophenyl	CH ₂	cyclooctyl
621	R	4-pyridinyl	4-fluorophenyl	CH ₂	cyclooctyl
622	S		4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
623	R	H	4-fluorophenyl	absent	cyclooctyl
624	R	n-butyl	4-fluorophenyl	absent	cyclooctyl
625	R	3-nitrobenzyl	4-fluorophenyl	absent	cyclooctyl
626	R		4-fluorophenyl	absent	cyclooctyl
627	R	4-pyridinyl	4-fluorophenyl	absent	cyclooctyl
628	R	4-methoxycarbonyl-benzyl	4-fluorophenyl	absent	cyclooctyl
629	R	1-[2-(3H-imidazol-4-yl)-ethyl]	4-fluorophenyl	absent	cyclooctyl

TABLE 1-continued

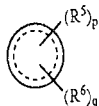
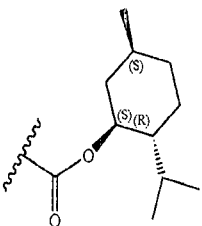
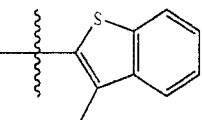
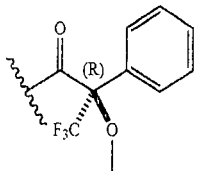
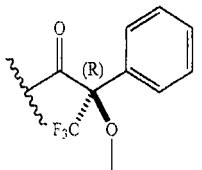
ID #	*	R ²	R ³	(L ¹) _m	
630	—		4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
631	R	C(O)O-t-butyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
632	R	H	4-fluorophenyl	CH(CH ₃)	
633	S	dimethylamino-n-propyl	4-fluorophenyl	CH ₂	cyclooctyl
634	S	3-hydroxy-n-propyl	4-fluorophenyl	CH ₂	cyclooctyl
635	R	3-hydroxy-n-propyl	4-fluorophenyl	CH ₂	cyclooctyl
636	R	dimethylamino-n-propyl	4-fluorophenyl	CH ₂	cyclooctyl
637	S	3-hydroxy-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
638	S	dimethylamino-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
639	R	3-hydroxy-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
640	R	H	phenyl	absent	1S-(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl
641	S	3-methoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
642	S	3-hydroxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
643	R	3-hydroxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
644	R	3-methoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
645	R		4-fluorophenyl	absent	R-1-acenaphthenyl
646	S		4-fluorophenyl	absent	R-1-acenaphthenyl

TABLE 1-continued

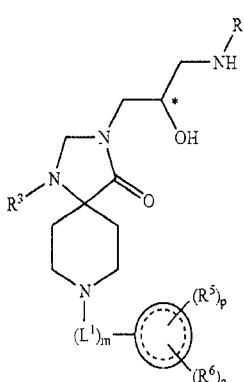
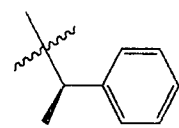
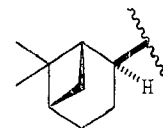
ID #	*	R ²	R ³	(L ¹) _m	
647	R	dimethylamino-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
648	S	methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
649	S	3-hydroxy-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
650	S	3-methoxy-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
651	R	3-hydroxy-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
652	R	3-methoxy-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
653	S	dimethylamino-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
654	S	methylamino-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
655	S	methylamino-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
656	R	methylamino-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
657	R	methylamino-n-propyl	4-fluorophenyl	CH ₂	cyclooctyl
658	S	methylamino-n-propyl	phenyl	absent	1S-(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl
659	S	H	phenyl	absent	1S-(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl
660	R	methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
661	R	methylamino-ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
662	R	1-(4-ethoxycarbonyl-piperidinyl)	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
663	R		4-fluorophenyl	absent	S-1-acenaphthenyl
664	R	methylamino-n-propyl	4-fluorophenyl	CH ₂	
665	R	t-butoxycarbonyl-amino-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
666	R	dimethylamino-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
667	R	N-methyl-N-t-butoxycarbonyl-amino-ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)

TABLE 2

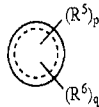
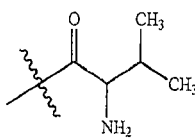
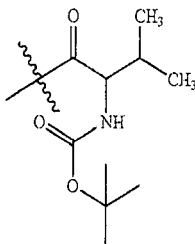
ID #	*	R ¹	R ²	R ³	(L ¹) _m	
54	S	n-butyl	benzyl	phenyl	absent	(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-2-yl
55	S	ethyl	4-methyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
56	S	t-butyl	benzyl	4-fluorophenyl	absent	1-acenaphthenyl
57	S	ethyl	4-methyl benzyl	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
58	S	ethyl	4-methyl benzyl	4-fluorophenyl	CH ₂ CH ₂	phenyl
59	S	t-butyl	benzyl	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
60	S	t-butyl	benzyl	4-fluorophenyl	CH ₂ CH ₂	phenyl
61	Rac	ethyl	4-methyl benzyl	phenyl	absent	1-acenaphthenyl
62	Rac	t-butyl	benzyl	phenyl	absent	1-acenaphthenyl
63	S	2-(dimethyl amino)ethyl	benzyl	4-fluorophenyl	CH ₂	cyclooctyl
64	S	n-butyl	benzyl	4-fluorophenyl	CH ₂	cyclooctyl
65	S	benzyl	2-phenyl-ethyl	4-fluorophenyl	CH ₂	cyclooctyl
78	S		4-methyl benzyl	4-fluorophenyl	CH ₂	cyclooctyl
79	S		4-methyl benzyl	4-fluorophenyl	CH ₂	cyclooctyl
250	S	t-butyl	benzyl	4-fluoro phenyl	CH ₂	1-naphthyl
252	S	ethyl	4-methyl benzyl	4-fluorophenyl	CH ₂	1-naphthyl
256	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	1-naphthyl
258	S	ethyl	4-methyl benzyl	4-fluorophenyl	CH ₂	2-naphthyl
260	S	t-butyl	benzyl	4-fluorophenyl	CH ₂	2-naphthyl
263	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	2-naphthyl
264	S	ethyl	4-methyl benzyl	4-fluorophenyl	CH ₂	4-chlorophenyl
266	S	t-butyl	benzyl	4-fluorophenyl	CH ₂	4-chlorophenyl
270	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	4-chlorophenyl
275	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
280	S	n-butyl	benzyl	4-fluorophenyl	CH ₂	2,3,4,5,6-pentamethyl-phenyl
283	S	methyl	3-(2-pyridyl)-n-propyl	4-fluorophenyl	CH ₂	cyclooctyl

TABLE 2-continued

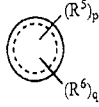
ID #	*	R ¹	R ²	R ³	(L ¹) _m	
289	S	benzyl	(1S,2S)-1-hydroxy-cyclopent-2-yl-methyl	4-fluorophenyl	CH ₂	cyclooctyl
290	S	benzyl	(1S,2S)-1-hydroxy-cyclohex-2-yl-methyl	4-fluorophenyl	CH ₂	cyclooctyl
291	S	benzyl	(1S,2S)-1-hydroxy-cyclohept-2-yl-methyl	4-fluorophenyl	CH ₂	cyclooctyl
294	S	ethyl	4-methyl benzyl	4-fluorophenyl	CH ₂	5-phenyl-2-thienyl
295	Rac	methyl	2-(3,4-dimethoxy-phenyl)ethyl	phenyl	absent	1-acenaphthenyl
299	R	t-butyl	benzyl	4-fluorophenyl	absent	1-acenaphthenyl
305	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
313	S	benzyl	2-phenylethyl	4-fluorophenyl	absent	1-acenaphthenyl
339	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
340	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	S-1-acenaphthenyl
362	S	benzyl	benzyl	4-fluorophenyl	absent	1-acenaphthenyl
364	S	methyl	2-(2-pyridyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
389	R	t-butyl	benzyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
391	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
394	S	ethyl	4-methyl benzyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
395	S	t-butyl	benzyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
399	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
423	R	methyl	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
428	R	methyl	methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
429	R	methyl	ethyl	4-fluorophenyl	absent	S-1-acenaphthenyl
432	S	methyl	methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
433	S	methyl	ethyl	4-fluorophenyl	absent	S-1-acenaphthenyl
434	R	methyl	ethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
435	S	methyl	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
436	S	methyl	ethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
439	S	methyl	methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
440	S	methyl	ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
441	R	methyl	methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
442	R	methyl	ethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
455	S	4-methyl-benzyl	6-methylthio-2-pyridyl-carbonyl	4-fluorophenyl	CH ₂	cyclooctyl
456	S	n-butyl	benzyl	4-fluorophenyl	CH ₂	2-trifluoromethyl-6-chloro-phenyl
457	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH ₂	2-trifluoromethyl-6-chloro-phenyl
459	S	benzyl	2-(dimethyl-amino)ethyl	4-fluorophenyl	CH ₂	2-trifluoromethyl-6-chloro-phenyl
462	R	ethyl	4-methyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
668	S	ethyl	phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
669	S	methyl	phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
670	S	ethoxy-carbonyl-methyl	benzyl	4-fluorophenyl	CH ₂	3,5-bis-trifluoromethyl-phenyl

TABLE 2-continued

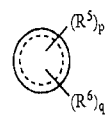
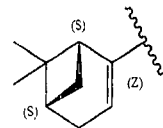
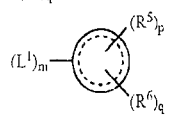
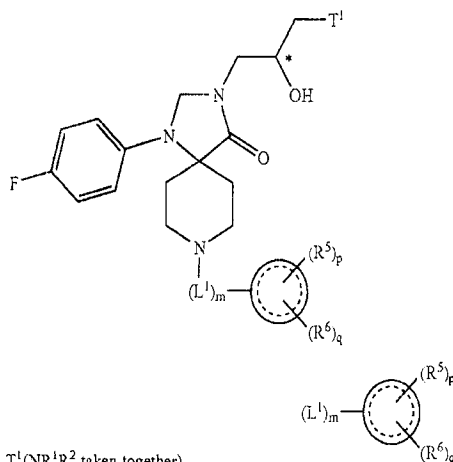
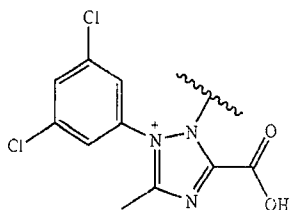
ID #	*	R ¹	R ²	R ³	(L ¹) _m	
671	S	n-butyl	benzyl	4-fluorophenyl	CH ₂	3,5-bis-tri-fluoromethyl-phenyl
672	S	1-phenyl-ethyl	benzyl	4-fluorophenyl	CH ₂	3,5-bis-tri-fluoromethyl-phenyl
673	S	2-(3,4-dimethoxy-phenyl)-ethyl	methyl	4-fluorophenyl	CH ₂	3,5-bis-tri-fluoromethyl-phenyl
674	S	(dimethyl-amino)-ethyl	benzyl	4-fluorophenyl	CH ₂	3,5-bis-tri-fluoromethyl-phenyl
675	S	2-(3,4-dimethoxy-phenyl)-ethyl	methyl	4-fluorophenyl	absent	cyclooctyl
676	S	benzyl	n-butyl	4-fluorophenyl	absent	cyclooctyl
677	S	benzyl	n-butyl	4-fluorophenyl	CH ₂	
678	R	2-(3,4-dimethoxy-phenyl)-ethyl	methyl	4-fluorophenyl	CH ₂	cyclooctyl
679	S	t-butoxy-carbonyl	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
680	S	t-butoxy-carbonyl	methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
681	R	amino-n-propyl	methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)

TABLE 3

ID #	*	T ¹ (NR ¹ R ² taken together)	
66	S	1-(4-(3-trifluoromethyl-phenyl)-piperazinyl)	cyclooctyl-methyl
67	S	1-(4-piperidinyl-piperidinyl)	cyclooctyl-methyl
68	S	1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl)	cyclooctyl-methyl



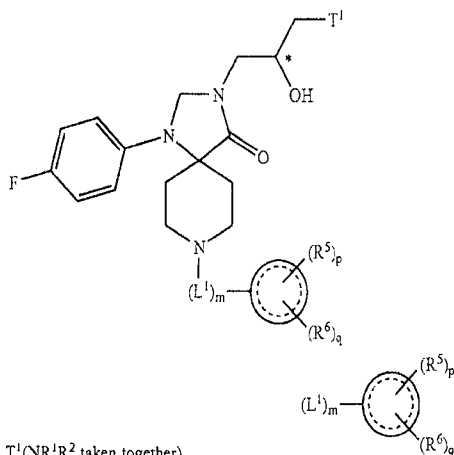
ID #	*	T¹(NR¹R² taken together)	
69	S	1-(3-(diethylaminocarbonyl)-piperidinyl)	cyclooctyl-methyl
70	S	1-(2,3-dihydro-1H-pyrrolyl)	cyclooctyl-methyl
71	S	1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl)	cyclooctyl-methyl
72	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	cyclooctyl-methyl
73	S	1-(4-t-butoxycarbonyl-piperazinyl)	cyclooctyl-methyl
74	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	cyclooctyl-methyl
75	S	4-(2,6-dimethyl-morpholinyl)	cyclooctyl-methyl
76	S	1-(4-benzyl-piperazinyl)	cyclooctyl-methyl
115	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
160	R	1-(4-t-butoxycarbonyl-piperazinyl)	2-(2-(2-thienyl)-phenyl)ethyl
165	S	1-(4-t-butoxycarbonyl-piperazinyl)	2-(2-(2-thienyl)-phenyl)ethyl
166	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
181	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
183	R	1-pyrrolidinyl	2-(2-(2-thienyl)-phenyl)ethyl
188	R	1-(4-ethoxycarbonyl-piperidinyl)	2-(2-(2-thienyl)-phenyl)ethyl
257	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
284	S	1-(2S-(phenylamino-methyl)-pyrrolidinyl)	cyclooctyl-methyl
682	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	3,5-bis-trifluoromethyl-benzyl
683	S	1-[4-(3-trifluoromethyl-phenyl)-piperazinyl]	3,5-bis-trifluoromethyl-benzyl
684	S	1-(4-ethoxycarbonyl-piperidinyl)	3,5-bis-trifluoromethyl-benzyl
685	S	1-(2,3-dihydro-pyrrolidinyl)	3,5-bis-trifluoromethyl-benzyl
686	S	3-(diethylaminocarbonyl)-piperidinyl	3,5-bis-trifluoromethyl-benzyl
687	S		cyclooctyl



688	R	1-(3,4-dihydroxy-2,5-bis-hydroxymethyl-pyrrolidinyl)	cyclooctyl
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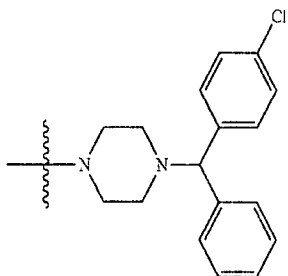
73

TABLE 3-continued



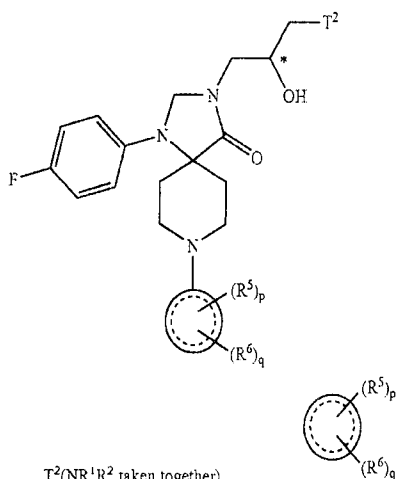
ID #	*	T¹(NR¹R² taken together)	
689	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	cyclooctyl

690 R



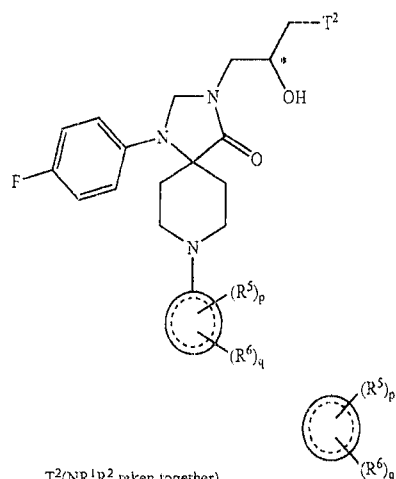
cyclooctyl

TABLE 4



ID #	*	T²(NR¹R² taken together)	
296	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-acenaphthenyl
332	S	1-(4-benzyl-piperazinyl)	1-acenaphthenyl
333	S	1-(4-(3-trifluoromethyl-phenyl)-piperazinyl)	1-acenaphthenyl
334	S	1-(4-(1-piperidinyl)-piperidinyl)	1-acenaphthenyl
335	S	1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl)	1-acenaphthenyl
336	S	1-(3-(diethylaminocarbonyl)-	1-acenaphthenyl

TABLE 4-continued



ID #	*	T ² (NR ¹ R ² taken together)		(R ⁵) _q
60	337	S	1-(4-[[4-(chlorophenyl)-phenyl-methyl]-piperazinyl])	1-acenaphthenyl
	360	S	1-(4-ethoxycarbonyl-piperidinyl)	1-acenaphthenyl
	377	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-acenaphthenyl
	382	R	1-imidazolyl	1-acenaphthenyl
65	388	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-(8-methyl-naphthyl)

75

TABLE 4-continued

ID #	*	T ² (NR ¹ R ² taken together)	
445	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-acenaphthenyl
465	S	1-piperidinyl	R-1-acenaphthenyl
691	S	1-morpholinyl	R-1-acenaphthenyl
692	S	1-pyrrolidinyl	R-1-acenaphthenyl
693	R	1-(4-ethoxycarbonyl-piperidinyl)	R-1-acenaphthenyl
694	R	1-(4-phenyl-piperidinyl)	R-1-acenaphthenyl
695	R	1-(3-hydroxymethyl-piperidinyl)	R-1-acenaphthenyl
696	R	1-(3-ethoxycarbonyl-piperidinyl)	R-1-acenaphthenyl
697	R	1-piperidinyl	R-1-acenaphthenyl
698	R	1-pyrrolidinyl	R-1-acenaphthenyl
699	S	1-(3,5-dimethyl-piperidinyl)	R-1-acenaphthenyl
700	S	1-(4-phenyl-piperidinyl)	R-1-acenaphthenyl
701	S	1-(4-ethoxycarbonyl-piperidinyl)	R-1-acenaphthenyl
702	S	1-(3-hydroxymethyl-piperidinyl)	R-1-acenaphthenyl
703	R	1-(3,5-dimethyl-piperidinyl)	R-1-acenaphthenyl
704	S	1-pyrrolidinyl	1-(8-methyl-naphthyl)
705	R	1-pyrrolidinyl	1-(8-methyl-naphthyl)
706	R	1-(3-(R)-hydroxy-pyrrolidinyl)	1-(8-methyl-naphthyl)
707	R	1-(3-hydroxy-piperidinyl)	1-(8-methyl-naphthyl)
708	R	1-(3-(R)-dimethylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
709	R	1-(4-hydroxy-piperidinyl)	1-(8-methyl-naphthyl)
710	R	1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
711	R	1-(4-t-butoxycarbonylamino-piperidinyl)	1-(8-methyl-naphthyl)
712	R	1-(3-hydroxy-pyrrolidinyl)	1-(8-methyl-naphthyl)
713	R	1-(4-pyrrolidinyl-piperidinyl)	1-(8-methyl-naphthyl)
714	R	1-(3-(S)-hydroxy-pyrrolidinyl)	1-(8-methyl-naphthyl)
715	R	1-(3-(S)-ethylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
716	R	1-(3-(R)-amino-pyrrolidinyl)	1-(8-methyl-naphthyl)
717	R	1-(3-(S)-amino-pyrrolidinyl)	1-(8-methyl-naphthyl)
718	R	1-(4-dimethylamino-piperidinyl)	1-(8-methyl-naphthyl)

76

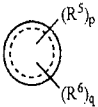
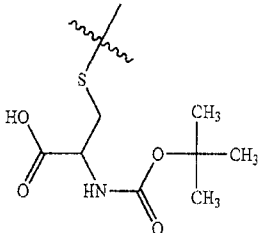
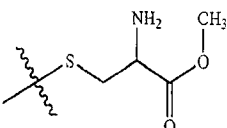
TABLE 4-continued

ID #	*	T ² (NR ¹ R ² taken together)	
719	R	1-(3-(R)-methylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
720	R	1-(3-(S)-methylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
721	R	1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl)	1-(8-methyl-naphthyl)

TABLE 5

ID #	*	R ²	(L ¹) _m	
100	R	4-fluorophenyl	CH ₂	cyclooctyl
101	S	4-fluorophenyl	absent	1-acenaphthenyl
102	R	4-fluorophenyl	CH ₂ CH ₂	phenyl
103	R	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
104	Rac	phenyl	absent	1-acenaphthenyl
179	R	phenyl	CH ₂ CH ₂	2-(2-thienyl)-phenyl
447	R	4-fluorophenyl	CH ₂	cyclooctyl

TABLE 6

ID #	*	X	R ³	(L ¹) _m	
105	R	2-(3,4-dimethoxyphenyl)-ethyloxy	4-fluorophenyl	CH ₂	cyclooctyl
106	R	2-(3,4-dimethoxyphenyl)-ethyloxy	phenyl	CH ₂ CH ₂	2-(2-thienyl)-phenyl
107	R	3-methylphenylthio	phenyl	CH ₂ CH ₂	2-(2-thienyl)-phenyl
108	R	3-methylphenylthio	4-fluorophenyl	CH ₂	cyclooctyl
178	S		phenyl	CH ₂ CH ₂	2-(2-thienyl)-phenyl
460	R		4-fluorophenyl	CH ₂	cyclooctyl

40

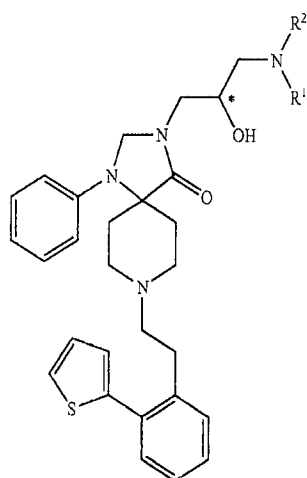
TABLE 7

ID No.	*	R ¹	R ²
110	Rac	H	3-(4-morpholinyl)-n-propyl
111	S	H	3-(4-morpholinyl)-n-propyl

TABLE 7-continued

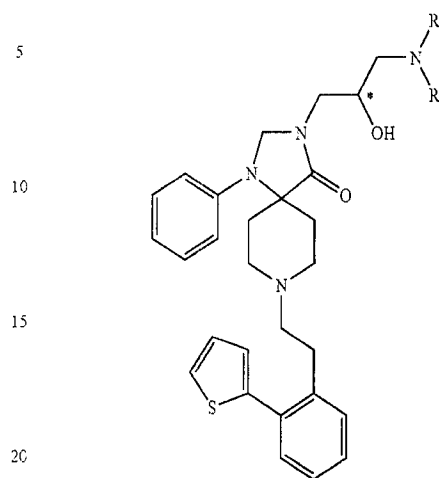
ID No.	*	R ¹	R ²
112	R	H	3-(4-morpholinyl)-n-propyl
113	S	H	3-chlorobenzyl

TABLE 7-continued



ID No.	*	R ¹	R ²
114	S	H	2-ethoxybenzyl
116	S	H	(2,5-dimethoxy-2,5-dihydro-fur-2-yl)-methyl
117	S	n-butyl	benzyl
118	S	H	2,5-difluorobenzyl
119	S	H	2-phenyl-ethyl
120	S	H	2-(5-bromo-pyridyl)
121	S	H	3-iodobenzyl
122	S	H	2,2,2-trifluoroethyl
123	S	H	3-nitrobenzyl
124	S	H	3,4-difluorobenzyl
125	S	H	3-bromobenzyl
126	S	H	4-chlorobenzyl
127	S	H	4-methoxybenzyl
128	S	H	3,4,5-trimethoxybenzyl
129	S	H	2-(2-thienyl)ethyl
130	S	H	3-methylbenzyl
131	S	H	2-methoxybenzyl
132	S	H	benzyl
133	S	H	4-bromobenzyl
134	S	H	3,5-di(trifluoromethyl)benzyl
135	S	H	2-(3-methoxyphenyl)ethyl
136	S	benzyl	2-phenylethyl
137	R	H	2-bromobenzyl
138	R	H	2-(4-bromophenyl)ethyl
139	R	H	4-(N,N-dimethylamino)benzyl
140	R	H	4-methylbenzyl
141	R	H	2-methylbenzyl
142	R	H	2-(6-fluoro-2-indolyl)ethyl
143	R	H	3-fluorobenzyl
144	R	H	3-methoxybenzyl
145	R	H	2-(4-methoxyphenyl)ethyl
146	R	H	2-trifluoromethylbenzyl
147	R	H	2-(4-imidazolyl)ethyl
148	R	H	3,5-dimethoxybenzyl
149	R	H	n-butyl
150	R	H	2-pyridyl-methyl
151	R	H	2-(3,4-dimethoxyphenyl)ethyl
152	R	H	2-fluorobenzyl
153	R	H	3-trifluoromethylbenzyl
154	R	H	4-pyridyl
155	R	H	4-trifluoromethoxybenzyl
156	R	H	2-phenyloxy-ethyl
157	R	H	1-naphthyl-methyl
158	R	H	4-fluorobenzyl
159	R	H	4-trifluoromethylbenzyl
161	R	H	4-pyridyl-methyl
162	R	H	2,4-dichlorobenzyl

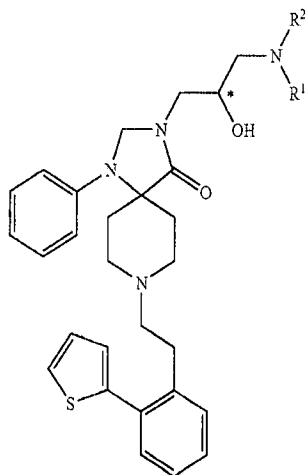
TABLE 7-continued



ID No.	*	R ¹	R ²
163	S	H	2-ethoxybenzyl
164	S	benzyl	benzyl
167	S	H	1-(3,4-methylenedioxypheyl)methyl
168	S	benzyl	ethoxycarbonylmethyl
169	S	H	2-phenyl-cyclopropyl
170	S	H	4-methoxycarbonylbenzyl
171	S	benzyl	2-(N,N-dimethylamino)ethyl
173	S	methyl	benzyl
174	S	ethyl	benzyl
175	R	benzyl	carboxymethyl
176	R	benzyl	2-(N,N-dimethylamino)ethyl
177	R	n-butyl	benzyl
180	R	H	2-phenyl-cyclopropyl
182	R	H	4-methoxycarbonylbenzyl
187	R	H	2-(2,5-dimethoxy-2,5-dihydro-fur-2-yl)-methyl
189	R	H	2,4-dimethoxybenzyl
190	R	H	4-biphenyl
191	R	benzyl	ethoxycarbonylmethyl
192	R	H	4-methoxybenzyl
193	S	H	2-methylbenzyl
194	S	H	3,5-dimethoxybenzyl
197	S	H	4-pyridyl
198	S	H	2,4-dichlorobenzyl
203	S	H	3,4-dimethoxybenzyl
204	R	H	4-bromobenzyl
205	R	H	3-methylbenzyl
206	R	H	2-(2-thienyl)-ethyl
208	S	H	3-nitrobenzyl
209	S	H	2-bromobenzyl
210	S	H	2-(4-imidazolyl)-ethyl
211	S	H	2-(phenoxy)-ethyl
215	S	H	2,3-dimethoxybenzyl
216	S	H	adamantanylmethyl
217	S	H	n-propyl
218	S	H	n-propyl

81

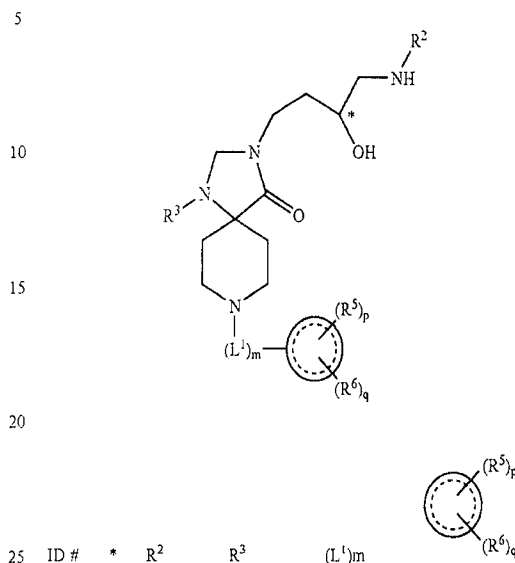
TABLE 7-continued



ID No.	*	R ¹	R ²
219	S	n-propyl	n-propyl
220	S	benzyl	benzyl
224	S	H	3-methoxybenzyl
225	S	H	3-pyridyl-methyl
227	S	H	2,4-difluorobenzyl
228	R	H	2-methoxybenzyl
229	S	H	3-(phenyl)-n-propyl
230	S	benzyl	2-phenylethyl

82

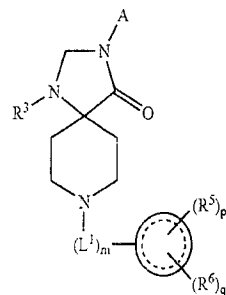
TABLE 8



ID #	*	R ²	R ³	(L ¹) _m	(R ⁵) _p (R ⁶) _q
722	S	H	4-fluorophenyl	absent	R-1-acenaphthenyl

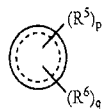
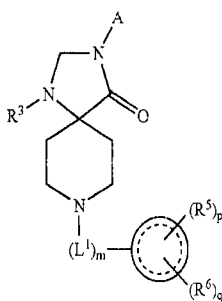
Representative intermediates in the preparation of the compounds of the present invention are as listed in Tables 9 and 10. Wherein Table 9, A is listed as oxarinyl-methyl with no indication of the stereo-configuration, the oxarinyl-methyl group was present as racemate.

TABLE 9



ID #	A	R ³	(L ¹) _m	(R ⁵) _p (R ⁶) _q
500	H	4-fluorophenyl	absent	1-acenaphthenyl
501	H	4-fluorophenyl	CH ₂ -CH(CH ₃)-CH ₂	phenyl
502	H	4-fluorophenyl	CH ₂ CH ₃	
503	H	4-fluorophenyl	CH ₂ CH ₂	phenyl
504	H	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
505	H	4-fluorophenyl	C(O)O-1-butyl	
506	H	4-fluorophenyl	CH ₂	2-naphthyl
507	H	4-fluorophenyl	CH ₂	1-naphthyl
508	H	4-fluorophenyl	CH ₂	4-chlorophenyl
521	H	4-fluorophenyl	CH ₂	4-quinolyl
522	H	4-fluorophenyl	CH ₂	8-quinolyl

TABLE 9-continued



ID #	A	R ³	(L ¹) _m	
544	H	4-fluorophenyl	absent	1,3,4-trihydro-2-naphthyl
546	H	4-fluorophenyl	CH ₂	5-phenyl-2-thienyl
547	H	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
548	H	4-fluorophenyl	CH ₂	1-(4-methyl-naphthyl)
549	H	4-fluorophenyl	absent	2-hydroxy-cycloheptyl
551	H	4-fluorophenyl	CH ₂	1-(2-methyl-naphthyl)
555	H	4-fluorophenyl	absent	R-1-acenaphthenyl
556	H	4-fluorophenyl	absent	S-1-acenaphthenyl
509	oxiranylmethyl	phenyl	absent	1-acenaphthenyl
510	R-oxiranylmethyl	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
511	R-oxiranylmethyl	4-fluorophenyl	CH ₂ CH ₂	phenyl
512	oxiranylmethyl	4-fluorophenyl	absent	1-acenaphthenyl
513	R-oxiranylmethyl	4-fluorophenyl	CH ₂	4-chlorophenyl
514	R-oxiranylmethyl	4-fluorophenyl	CH ₂	1-naphthyl
516	R-oxiranylmethyl	4-fluorophenyl	C(O)O-t-butyl	absent
517	S-oxiranylmethyl	4-fluorophenyl	O(O)O-t-butyl	absent
518	oxiranylmethyl	phenyl	CH ₂ CH ₂	2-(2-thienyl) phenyl
519	S-oxiranylmethyl	phenyl	CH ₂ CH ₂	2-(2-thienyl) phenyl
520	R-oxiranylmethyl	phenyl	CH ₂ CH ₂	2-(2-thienyl) phenyl
540	R-oxiranylmethyl	4-fluorophenyl	CH ₂	cyclooctyl
541	R-oxiranylmethyl	4-fluorophenyl	CH ₂	5-phenyl-2-thienyl
542	S-oxiranylmethyl	4-fluorophenyl	CH ₂	2-naphthyl
543	S-oxiranylmethyl	4-fluorophenyl	CH ₂ CH ₃	absent
550	S-oxiranylmethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
552	methoxy-carbonyl methyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
553	R-oxiranylmethyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
554	R-2,3-dihydroxy-n-propyl	4-fluorophenyl	CH ₂	1-(8-methyl-naphthyl)
564	S-oxiranylmethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
565	R-oxiranylmethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
566	S-oxiranylmethyl	4-fluorophenyl	absent	S-1-acenaphthenyl
567	R-oxiranylmethyl	4-fluorophenyl	absent	S-1-acenaphthenyl
568	2R-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	1-acenaphthenyl
569	2R-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
570	2S-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
571	2R-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
572	H	4-fluorophenyl	CH ₂	
573	H	4-fluorophenyl	CH ₂	3-(2H)-chromenyl
576	oxiranylmethyl	phenyl	absent	1-acenaphthenyl
578	R-oxiranylmethyl	4-fluorophenyl	CH ₂	2-trifluoromethyl-6-chloro-phenyl
579	3-chloro-2S-hydroxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
580	S-oxiranylmethyl	4-fluorophenyl	CH ₂	cyclooctyl
581	H	phenyl	CH ₂ CH ₂	2-(2-thienyl)-phenyl

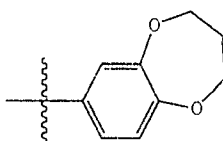


TABLE 9-continued

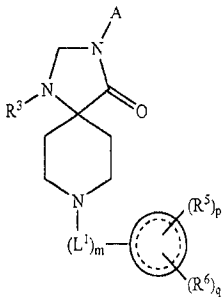
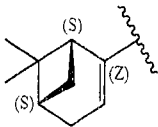
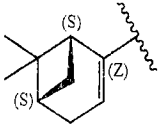
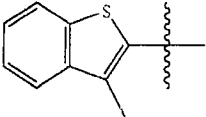
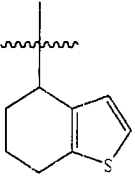
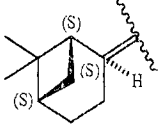
ID #	A	R ³	(L ¹) _m	
582	H	4-fluorophenyl	CH ₂	cyclooctyl
583	H	4-fluorophenyl	CH ₂	2,3,4,5,6-pentamethyl-phenyl
584	R-oxiranylmethyl	4-fluorophenyl	CH ₂	2,3,4,5,6-pentamethyl-phenyl
723	R-oxiranylethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
725	R-oxiranylmethyl	4-fluorophenyl	CH ₂	2,3,4,5,6-pentamethylphenyl
726	H	4-fluorophenyl	CH ₂	
727	R-oxiranylmethyl	4-fluorophenyl	CH ₂	
728	H	4-fluorophenyl	CH ₂	1-(8-methyl-1,2,3,4-tetrahydro-naphthyl)
729	H	4-fluorophenyl	CH(CH ₃)	
730	H	4-fluorophenyl	absent	
731	S-oxiranylmethyl	4-fluorophenyl	absent	cyclooctyl
732	H	4-fluorophenyl	CH ₂	
733	H	4-fluorophenyl	CH ₂	1-[8-methoxy]-naphthyl]
734	H	4-fluorophenyl	CH ₂	1-[8-hydroxymethyl]-naphthyl]
735	H	4-fluorophenyl	absent	cyclooctyl

TABLE 10

ID #	*	R ¹	R ²	W
523	R	ethyl	4-methylbenzyl	H
524	R	H	2-(4-morpholinyl)-ethyl	H
525	R	t-butyl	benzyl	H
526	R	H	2-(3,4-dimethoxy-phenyl)-ethyl	H
527	R	H	2-(3,4-methylenedioxy phenyl)-ethyl	H
528	R	H	2-(2-nitro-4,5-dimethoxy-phenyl)-ethyl	H
529	S	ethyl	4-methylbenzyl	H
530	S	H	2-(4-morpholinyl)-ethyl	H
531	S	t-butyl	benzyl	H
532	S	H	2-(3,4-dimethoxy-phenyl)-ethyl	H
533	S	H	2-(3,4-methylenedioxy phenyl)-ethyl	H
534	S	H	2-(2-nitro-4,5-dimethoxy-phenyl)-ethyl	H
535	S	ethyl	4-methylbenzyl	t-butoxy-carbonyl
536	R	ethyl	4-methylbenzyl	ethyl
537	R	H	2-(4-morpholinyl)-ethyl	ethyl
538	R	t-butyl	benzyl	ethyl
539	R	H	2-(3,4-dimethoxy-phenyl)-ethyl	ethyl

Molecular weights for representative compounds of the present invention exemplified in Tables 1-10 above were measured using a Micromass Platform LC-Electrospray Mass Spectrometer, Chemical Ionization Spectrometer HP5989A or Agilent LC/MSD Electrospray Mass Spectrometer with results listed in Table 11.

TABLE 11

ID #	Theor. MW	M/e[MH ⁺]
1	559.77	560.8
2	596.78	597.7
3	672.73	673.6
4	540.72	541.7
5	615.63	617.9
6	610.81	611.8
7	572.71	573.3
8	596.78	597.5
9	598.8	599.5
10	580.78	581.5
11	550.76	551.5
12	572.71	573.5
13	602.60	604.3
14	566.76	567.5
15	615.60	617.4
16	672.73	673.5
17	594.85	595.5
18	550.76	551.5
19	588.76	589.5
20	615.63	617.4
21	571.18	571.5
22	596.78	597.5
23	581.73	582.5
24	537.72	538.4
25	596.78	597.2
26	556.79	557.4
27	550.76	552.4

TABLE 11-continued

ID #	Theor. MW	M/e[MH ⁺]
28	540.72	541.5
29	604.73	605.5
30	629.65	630.5
31	605.62	607.3
32	537.72	538.4
33	604.73	605.4
34	566.76	567.5
35	566.76	567.7
36	523.69	523.9
38	610.81	611.5
39	537.72	538.5
40	586.79	587.4
41	550.76	551.4
42	551.75	551.5
43	626.81	627.4
44	615.63	616.4
45	596.78	597.3
46	605.62	607.4
47	587.70	588.3
48	638.70	639.3
49	610.81	611.4
50	539.63	540.3
51	590.74	591.3
52	621.00	622.0
53	569.00	570.0
54	620.88	621.5
55	606.70	607.3
56	620.80	621.3
57	578.81	579.5
58	558.74	559.3
59	592.84	593.4
60	572.77	573.3
61	588.00	589.0
62	602.00	603.0
63	607.28	608.3
64	592.84	593.5
65	640.88	641.5
66	659.81	660.1
67	597.86	598.2
68	649.85	650.1
69	613.86	614.3
70	498.68	499.5
71	716.38	717.4
72	562.77	563.5
73	615.83	616.4
74	622.82	623.2
75	544.75	545.4
76	605.84	606.2
78	649.89	650.2
79	750.01	751.5
100	592.77	593.8
101	620.70	621.3
102	572.70	573.3
103	592.77	593.3
104	602.70	603.0
105	611.79	612.4
106	655.86	656.4
107	597.84	598.4
108	553.78	554.6
110	617.85	618.3
111	617.85	618.3
112	617.85	618.3
113	615.24	615.3
114	624.85	625.3
115	606.83	607.3
116	632.82	633.3
117	636.90	637.4
118	616.78	617.3
119	594.80	595.3
120	646.65	648.2
121	706.68	707.2
122	572.69	573.3
123	625.79	626.3
124	616.77	617.3
125	659.68	661.2
126	615.30	615.3
127	610.82	611.3

US 7,081,463 B2

89

TABLE 11-continued

ID #	Theor. MW	M/e[MH ⁺]
128	670.87	671.3
129	600.85	601.2
130	594.82	595.3
131	610.82	611.3
132	580.79	581.2
133	659.69	661.2
134	716.79	717.2
135	624.85	625.3
136	684.94	685.3
137	659.69	661.2
138	673.72	675.3
139	623.86	624.4
140	594.82	595.4
141	594.82	595.4
142	651.85	652.3
143	598.78	599.3
144	610.82	611.3
145	624.85	625.3
146	648.80	649.3
147	584.76	585.3
148	640.85	641.3
149	546.77	547.3
150	581.78	582.3
151	654.87	655.5
152	598.78	599.3
153	648.79	649.3
154	567.75	568.3
155	664.79	665.3
156	610.82	611.3
157	630.85	631.3
158	598.78	599.3
159	648.80	649.3
160	659.89	660.4
161	581.78	582.3
162	649.68	651.1
163	759.11	759.1
164	670.82	671.4
165	659.89	660.5
166	666.88	667.4
167	624.80	625.4
168	666.88	667.4
169	606.83	607.5
170	638.83	639.4
171	651.92	653.0
173	594.80	595.8
174	608.85	609.9
175	638.83	639.6
176	651.92	652.9
177	636.90	637.6
178	694.91	695.8
179	636.90	637.6
180	606.83	607.9
181	666.88	667.8
182	638.83	639.8
183	544.76	545.7
187	632.82	633.9
188	630.85	631.9
189	640.85	641.9
190	642.86	643.8
191	666.88	667.8
192	610.82	611.9
193	594.82	595.8
194	640.85	641.9
197	567.75	568.8
198	649.68	651.6
203	640.85	641.7
204	659.69	662.0
205	594.82	595.9
206	600.85	601.7
208	625.79	626.8
209	659.69	661.2
210	584.79	585.8
211	610.82	611.8
215	640.85	641.7
216	759.11	759.7
217	638.92	639.8
218	532.75	533.6

90

TABLE 11-continued

ID #	Theor. MW	M/e[MH ⁺]
219	574.83	575.9
220	670.92	671.7
224	610.82	611.8
225	581.78	582.7
227	616.78	617.7
228	610.82	611.8
229	608.85	609.7
230	684.94	685.7
250	608.79	609.3
251	575.72	576.3
252	594.76	595.3
253	626.76	627.3
254	610.72	611.2
255	671.76	672.3
256	640.79	641.4
257	638.77	639.3
258	594.76	595.3
259	575.72	576.3
260	608.79	609.3
261	626.76	627.3
262	610.72	611.2
263	640.78	641.4
264	579.15	579.3
265	560.10	560.2
266	593.17	593.3
267	611.15	611.2
268	595.10	595.2
269	656.14	656.2
270	625.17	625.3
271	622.72	623.2
275	652.80	653.4
276	683.79	684.3
279	650.88	651.3
280	628.88	629.2
281	566.77	567.5
282	743.95	744.1
283	565.75	566.4
284	605.85	605.9
285	604.86	605.3
289	634.89	635.3
290	648.91	649.2
291	662.94	663.3
292	658.84	659.2
293	607.80	608.3
294	626.84	627.3
295	634.82	635.4
296	650.80	651.3
298	587.74	588.3
299	620.82	621.4
300	638.79	639.3
305	652.82	653.3
307	624.76	625.3
308	609.71	610.3
309	619.79	620.3
310	626.78	627.3
311	554.67	555.4
312	690.61	691.2
313	668.86	669.3
314	600.69	601.3
315	643.61	643.6
316	599.15	599.2
317	594.74	595.3
318	594.74	595.3
319	700.71	701.2
320	654.79	655.3
321	582.70	583.3
322	594.74	595.3
323	608.76	609.3
324	624.76	625.3
325	578.74	579.3
326	592.76	593.4
327	551.67	552.3
328	648.71	649.3
329	594.74	595.3
330	578.74	579.0
331	624.76	625.3
332	633.82	634.3

US 7,081,463 B2

91

TABLE 11-continued

ID #	Theor. MW	M/e[MH+]
333	687.79	688.3
334	625.84	626.4
335	677.83	678.3
336	641.84	642.5
337	744.36	744.3
338	643.90	644.4
339	652.82	653.4
340	652.82	653.4
341	578.74	579.3
342	600.69	601.3
343	633.60	633.2
344	632.71	634.0
345	564.71	565.3
346	582.70	583.3
347	632.71	634.0
348	622.75	623.2
349	624.76	625.3
350	599.15	599.2
351	608.76	609.3
352	643.10	643.2
353	578.74	579.3
354	584.72	583.3
355	643.61	645.2
356	608.72	609.0
358	600.69	601.0
360	614.77	615.0
362	654.84	655.3
364	593.75	594.2
365	657.63	659.2
366	565.70	566.2
367	654.79	655.3
368	633.60	635.2
370	609.71	610.3
371	614.77	615.3
372	584.76	595.3
373	632.71	633.3
374	743.03	743.6
375	579.72	580.3
376	565.70	566.2
377	650.80	651.3
378	551.67	552.2
379	551.67	552.2
380	581.70	582.2
381	551.67	552.3
382	525.63	526.2
383	565.70	566.2
385	640.81	641.4
386	640.81	641.4
387	589.76	590.4
388	652.82	653.4
389	622.83	623.4
390	624.76	625.3
391	654.83	655.3
392	596.75	597.3
393	553.69	554.2
394	608.81	609.4
395	622.83	623.4
396	589.76	590.4
398	596.75	597.3
399	654.83	655.3
418	624.76	625.3
419	551.67	552.3
420	474.58	475.2
421	551.67	552.3
422	476.6	477.3
423	502.64	503.3
424	474.58	475.2
425	488.61	489.3
426	474.58	475.2
427	488.61	489.3
428	502.64	503.3
429	516.66	517.3
430	474.58	475.2
431	488.61	489.3
432	502.64	503.3
433	516.66	517.3
434	516.66	517.3

92

TABLE 11-continued

ID #	Theor. MW	M/e[MH+]
435	502.64	503.3
436	516.66	517.3
437	488.61	489.3
438	476.6	477.3
439	504.65	505.4
440	518.68	519.3
441	504.65	505.4
442	518.68	519.3
443	504.61	505.2
444	518.64	519.3
445	650.80	651.3
446	622.75	623.2
447	592.78	593.4
448	594.74	595.3
451	743.95	744.1
452	580.75	581.5
453	446.61	447.9
454	502.72	503.2
455	701.95	702.0
456	661.19	662.5
457	693.19	694.0
458	591.05	592.0
459	676.20	677.4
460	564.77	565.2
461	683.79	684.3
462	606.79	607.3
463	580.71	581.3
464	593.75	594.3
465	542.70	543.3
500	401.49	402.2
501	367.47	368.2
502	277.34	278.2
503	353.44	354.2
504	373.52	374.2
505	349.41	372.0
506	389.48	390.1
507	389.48	390.1
508	373.86	374.1
509	439.56	440.2
510	409.51	410.2
511	429.58	430.3
512	457.55	458.3
513	429.93	430.2
514	445.54	446.3
516	405.47	428.3
517	405.47	428.3
518	473.65	474.1
519	473.65	474.1
520	473.65	474.1
521	390.45	391.2
522	390.45	391.0
523	454.58	455.0
524	435.54	436.0
525	468.61	469.0
526	486.58	487.0
527	470.54	471.0
528	531.58	532.0
529	454.48	544.0
530	435.54	436.0
531	468.61	469.0
532	486.58	488.0
533	470.54	471.0
534	531.58	532.0
535	554.70	555.3
536	482.65	483.3
537	463.60	464.3
538	496.67	497.4
539	514.65	515.2
540	429.58	430.5
541	477.61	478.2
542	445.54	446.3
543	333.41	334.2
544	379.48	380.2
546	421.54	422.1
547	403.50	404.2
548	403.50	404.2
549	361.46	362.3

71

TABLE 11-continued

ID #	Theor. MW	M/e[MH+]
550	459.57	460.2
551	403.50	404.2
552	475.57	476.2
553	459.57	460.2
554	477.58	478.2
555	401.49	402.1
556	401.49	402.1
564	457.55	458.3
565	457.55	458.3
566	457.55	458.3
567	457.55	458.3
568	503.62	504.3
569	503.62	504.3
570	503.62	504.3
571	503.62	504.3
572	411.48	412.2
573	393.47	394.2
576	439.56	438.3
578	497.92	498.9
579	494.01	494.2
581	417.58	418.1
582	373.52	374.1
583	409.55	410.5
584	465.62	466.1
600	550.68	551.7
601	693.87	694.9
602	568.67	569.7
603	610.74	611.7
604	564.71	565.7
605	593.75	594.8
606	514.65	515.7
607	696.76	697.8
608	625.59	626.6
609	639.62	640.6
610	717.82	718.8
611	565.7	566.7
612	565.7	566.7
613	565.7	566.7
614	570.73	571.7
615	692.76	693.8
616	432.59	433.6
617	509.67	510.7
618	533.7	534.7
619	456.61	457.6
620	446.61	447.6
621	523.7	524.7
622	692.76	693.8
623	432.59	433.6
624	488.69	489.7
625	567.71	568.7
626	701.03	702.0
627	509.67	510.7
628	580.75	581.8
629	526.7	527.7
630	658.86	659.9
631	576.72	577.7
632	496.65	497.7
633	531.76	532.8
634	504.69	505.7
635	504.69	505.7
636	531.76	532.8
637	532.66	533.7
638	559.73	560.7
639	532.73	533.7
640	474.65	475.7
641	546.69	547.7
642	532.66	533.7
643	532.66	533.7
644	546.69	547.7
645	690.74	691.7
646	690.74	691.7
647	559.73	560.7
648	490.63	491.6
649	534.68	535.7
650	548.71	549.7
651	534.68	535.7
652	235.13	236.1

TABLE 11-continued

ID #	Theor. MW	M/e[MH+]
653	430.5	431.5
654	545.71	546.7
655	547.72	548.7
656	547.72	548.7
657	517.74	518.7
658	545.77	546.8
659	474.65	475.7
660	490.63	491.6
661	533.7	534.7
662	631.8	632.8
663	578.74	579.7
664	529.75	530.8
665	633.81	634.8
666	561.75	562.8
667	633.80	634.2
668	578.74	579.7
669	564.71	565.7
670	724.73	725.7
671	694.74	695.7
672	742.79	743.8
673	726.74	727.7
674	709.76	710.8
675	610.82	611.8
676	578.82	579.8
677	602.84	603.8
678	564.74	565.7
679	645.82	646.8
680	647.84	648.8
681	547.72	548.7
682	664.67	665.7
683	761.71	762.7
684	688.69	689.7
685	600.58	601.6
686	715.76	716.8
687	688.66	689.7
688	578.73	579.7
689	608.8	609.8
690	702.36	703.4
691	544.68	545.7
692	528.68	529.7
693	614.77	615.8
694	618.8	619.8
695	572.73	573.7
696	614.77	615.8
697	542.7	543.7
698	528.68	529.7
699	570.76	571.8
700	618.8	619.8
701	614.77	615.8
702	572.73	573.7
703	570.76	571.8
704	530.69	531.7
705	530.69	531.7
706	546.69	547.7
707	560.72	561.7
708	573.76	574.8
709	560.72	561.7
710	645.82	646.8
711	659.85	660.9
712	546.69	547.7
713	613.83	614.8
714	546.60	547.7
715	573.76	574.8
716	545.71	546.7
717	545.71	546.7
718	587.79	588.8
719	559.73	560.7
720	559.73	560.7
721	659.85	660.9
722	488.61	489.6
723	471.58	472.6
725	465.62	466.6
726	383.51	384.5
727	439.58	440.6
728	407.54	408.5
729	423.56	424.6
730	385.51	386.5

TABLE 11-continued

ID #	Theor. MW	M _n (MH ⁺)
731	415.56	416.6
732	385.53	386.4
733	433.53	434.5
734	419.5	420.5
735	359.49	360.5

The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 5 to about 1000 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

The method of treating disorders mediated by the ORL-1 receptor described in the present invention may also be carried out using a pharmaceutical composition comprising

any of the compounds as defined herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 1 mg and 1000 mg, preferably about 10 to 500 mg, of the compound, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms may include suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compound of the present invention can also be administered via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhy-

97

droxyethylaspartamidophenol, or polyethyl-eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of disorders mediated by the ORL-1 receptor is required.

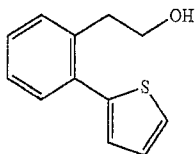
The daily dosage of the products may be varied over a wide range from 1 to 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.5, 1.0, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Preferably, the range is from about 0.1 mg/kg to about 10 mg/kg of body weight per day, and especially from about 0.5 mg/kg to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

EXAMPLE 1

2-Thienylphenyl-2-ethanol



3-Bromophenethyl alcohol (4 ml, 29.8 mmol) was dissolved in 1,2-dimethoxyethane (225 mL) and mixed with tetrakis(triphenylphosphine) palladium[0] (2.6 g, 2.25 mmol) at room temperature. The reaction mixture was then added to a solution of 2-thienyl-boronic acid (12.6 g, 99 mmol) and 1 N NaHCO₃ (90 mL). The reaction mixture was heated to reflux under nitrogen atmosphere for 48 hours. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was dried with MgSO₄, filtered through a plug of silica and the solvent was evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (30% EtOAc/hexane) to yield the title compounds as an oil.

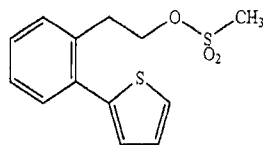
MS (chemical ionization)=221 (M+NH₄)

¹H NMR (300 MHz, CDCl₃) δ 1.3 (t, 1H), 3.0 (t, 2H), 3.75 (q, 2H), 7.0-7.4 (m, 7H)

98

EXAMPLE 2

Methane sulfonic acid 2-(2-thien-2-yl-phenyl)-ethyl ester



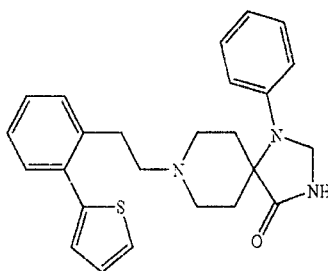
2-Thienylphenylethanol (13.6 mmol) and triethylamine (2.4 mL, 17.1 mmol) were dissolved in dichloromethane (50 mL). Methanesulfonylchloride 1.1 mL, 14 mmol) was then added slowly. The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was carefully partitioned with water and dichloromethane. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield the title compounds, which was used without further purification.

MS (chemical ionization)=300 (M+NH₄), 283 (MH⁺), 187,

¹H NMR (300 MHz, CDCl₃) δ 2.8 (s, 3H), 3.2 (t, 2H), 4.3 (t, 2H), 7.0 (m, 1H), 7.1 (m, 1H), 7.2-7.5 (m, 5H)

EXAMPLE 3

1-Phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #581



Methane sulfonic acid 2-(2-thien-2-yl-phenyl)-ethyl ester (23.14 mmol) was combined in NMP (100 mL) with 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (5.08 g, 22 mmol) and DIPEA (5.11 mL, 27.8 mmol) in a reaction tube which was sealed and heated to 70° C. overnight. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was dried with MgSO₄, filtered and the solvent was evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5% methanol/CH₂Cl₂) to yield the title compound as a solid.

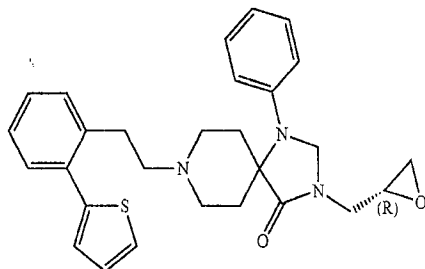
MS (electrospray)=418.1 (MH⁺), 313.0

¹H NMR (300 MHz, DMSO-d₆) δ 1.5 (d, 2H), 2.4 (m, 4H), 2.6 (m, 4H), 2.85 (m, 2H), 4.55 (s, 2H), 6.7-6.8 (m, 3H), 7.1-7.4 (m, 8H), 7.6 (s, 1H), 8.65 (s, 1H)

99

EXAMPLE 4

(R)-3-Oxiranylmethyl-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one
Compound #520



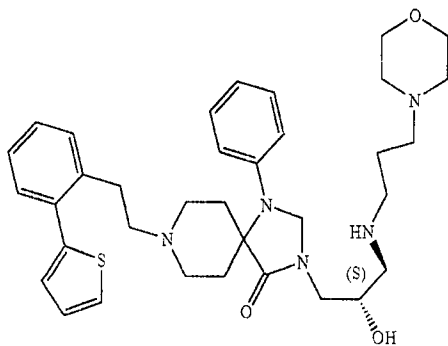
1-Phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one (0.7 g, 1.68 mmol) was dissolved in NMP (50 mL). To the mixture was then added sodium hydride (60% in mineral oil, 0.1, 2.52 mmol) and the reaction mixture stirred for 1 hour. S-(+)-epichlorohydrin (0.15 mL, 1.9 mmol) was then added to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned with saturated sodium bicarbonate and ethyl acetate. The organic layer was then partitioned with water. The organic layer was dried with $MgSO_4$, filtered and the solvent was evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (80% EtOAc/hex) to yield the title compound as an oil.

MS (electrospray)=474.1 (MH⁺)

¹H NMR (300 MHz, $CDCl_3$) δ 1.6 (t, 2H), 2.5–3.0 (m, 12H), 3.1–3.2 (m, 2H), 4.05 (d, 1H), 4.7 (d, 1H), 4.8 (d, 1H), 6.8 (m, 2H), 7.0 (m, 1H), 7.2–7.4 (m, 9H).

EXAMPLE 5

3-[2-(S)-Hydroxy-3-(3-morpholin-4-yl-propylamino)-propyl]-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one
Compound #111



3-(R)-Oxiranylmethyl-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one (0.1 g, 0.21 mmol) was dissolved in absolute ethanol (2 mL), mixed with 3-aminopropyl morpholino (90 μ L, 0.63 mmol) and heated to 70° C. overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatog-

100

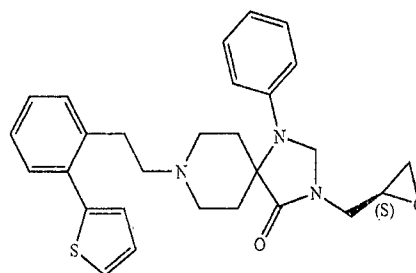
raphy (AcCN/water) to yield the title compounds as a trifluoroacetate salt, as a solid.

MS (electrospray)=618.3 (MH⁺)

¹H NMR (300 MHz, CD_3OD) δ 2.0 (d, 2H), 2.2 (m, 2H), 2.72–2.88 (m, 2H), 3.0–4.3 (m, 23H), 4.8–5.05 (m, 6H), 6.8–7.5 (m, 12H).

EXAMPLE 6

(S)-3-Oxiranylmethyl-1-phenyl-8-[2-(2-thienyl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one
Compound #519



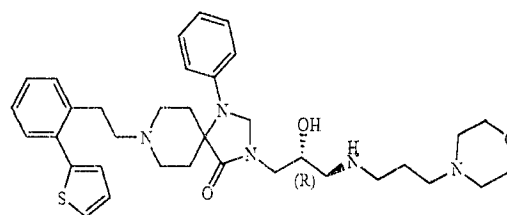
1-Phenyl-8-[2-(2-thienyl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one (0.13 g, 0.3 mmol) was dissolved in NMP (10 mL). To the mixture was then added sodium hydride (60% in mineral oil, 31 mg, 0.8 mmol) and the reaction mixture stirred for 1 hour. R-(-)-epichlorohydrin 927 μ L, 0.35 mmol) was then added to the reaction mixture, which was then stirred overnight at room temperature. The reaction mixture was partitioned with saturated sodium bicarbonate and ethyl acetate. The organic layer was then partitioned with water. The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (80% EtOAc/hexanes) to yield the title compound as an oil.

MS (electrospray)=474.1 (MH⁺)

¹H NMR (300 MHz, $CDCl_3$) δ 1.65 (t, 2H), 2.0 (q, 1H), 2.4 (t, 1H), 2.5–3.0 (m, 11H), 3.2 (m, 1H), 3.3 (t, 1H), 4.0 (d, 1H), 4.7 (d, 1H), 4.8 (d, 1H), 6.9 (m, 2H), 7.0 (m, 1H), 7.15–7.4 (m, 9H).

EXAMPLE 7

3-[2-(R)-hydroxy-3-(3-morpholin-4-yl-propylamino)-propyl]-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one
Compound #112



3-(S)-Oxiranylmethyl-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one (0.13 g, 0.27 mmol) was dissolved in absolute ethanol (2 mL), mixed with

101

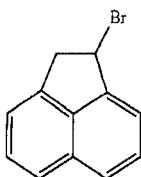
3-aminopropylmorpholino (100 μ L, 0.68 mmol) and heated with stirring at 70° C. overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (Acetonitrile/water) to yield the title compound as a trifluoroacetate salt as a solid.

MS (electrospray)=618.3 (MH⁺)

¹H NMR (300 MHz, CD₃OD) δ 2.0 (d, 2H), 2.2 (m, 2H), 2.75–2.9 (m, 2H), 3.0–4.3 (m, 23H), 4.8–5.05 (m, 6H), 6.8–7.5 (m, 12H).

EXAMPLE 8

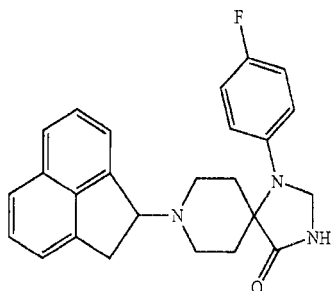
1-bromo-acenaphthene



Acenaphthen-1-ol (88 mol) was dissolved in diethyl ether (150 mL) and cooled down to 0° C. Phosphorous tribromide (3.2 mL, 35 mmol) was then added slowly under nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at room temperature and cooled to 0° C. The reaction mixture was partitioned with water and diethyl ether. The organic layer was dried over Na₂SO₄, filtered and the solvent evaporated in vacuo to yield the title compound as a yellow solid.

EXAMPLE 9

8-Acenaphthen-1-yl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one Compound # 500



1-Bromo-acenaphthene (20.5 g, 87.9 mmol) and 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (9.15 g, 36.6 mmol) were dissolved in N,N-dimethylformamide (190 mL). Potassium carbonate (15.15 g, 110 mmol) was then added and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned with water and diethyl ether. The title compound precipitated from the organic layer as an off-white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.68–7.66 (1H, m), 7.60 (1H, d, J=8.2 Hz), 7.53–7.49 (2H, m), 7.43 (1H, t, J=8.1 Hz), 7.26 (1H, d, J=7.8 Hz), 7.04–6.94 (4H, m), 6.67 (1H, br, s), 4.95 (1H, br, s), 4.66–4.63 (2H, m), 3.51 (1H, d), 3.34 (1H, dd, J=7.6 and 17.5 Hz), 3.13–2.94 (2H, m), 2.83 (1H, br, s), 2.43 (1H, br, a), 2.24 (1H, m), 1.80–1.66 (3H, m)

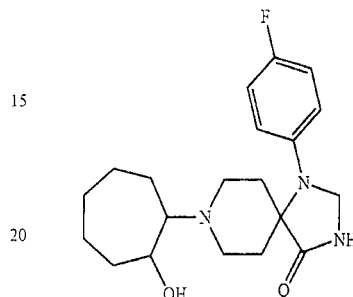
MS (ES⁺) m/z 402.1 (M+H)⁺

102

Chiral resolution: The racemate prepared as described above was resolved using a CHIRALCEL OD-H column with methanol as mobile phase and generated the two pure enantiomers R (RT=6.174 minutes, ee>99%) and S (RT=10.175 minutes, ee>99%).

EXAMPLE 10

1-(4-fluorophenyl)-8-(2-hydroxy-cycloheptyl)-1,3,8-triazaspiro[4.5]decan-4-one Compound #549



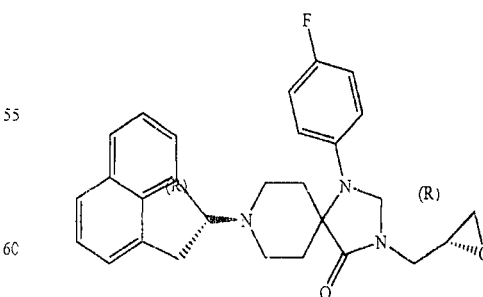
1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (0.15 g, 0.6 mmol) was dissolved in dichloromethane (1 mL) and 1,2-dichloromethane (0.25 mL) under a nitrogen atmosphere. The reaction mixture was then added slowly at 0° C. to 1.9M triethyl aluminum in toluene (0.315 mL, 0.6 mmol). After stirring for 30 minutes at room temperature, to the reaction mixture was added slowly a solution of 8-oxabicyclo[5.1.0]octane (68 mg, 0.6 mmol) in dichloromethane (16 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 13 days and then partitioned with 1N NaOH and DCM. The organic layer was dried over Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/DCM) to yield the title compound as an oil.

¹H NMR (300 MHz, CDCl₃) δ 7.05–6.88 (4H, m), 4.69 (s, 2H), 3.44–3.31 (2H, m), 2.96–2.88 (1H, m), 2.73–2.69 (1H, m), 2.56–2.53 (1H, m), 2.42–2.17 (3H, m), 2.11–2.02 (1H, m), 1.94–1.87 (1H, m), 1.78 (1H, d), 1.72–1.19 (11H, m)

MS (ES⁺) m/z 362.3 (M+H)⁺

EXAMPLE 11

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triazaspiro[4.5]decan-4-one Compound #556



(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5 g, 3.736 mmol) was dissolved in N,N-dimethylformamide (10.0 mL). To the reaction mixture was then added at 0° C. sodium hydride (60%

103

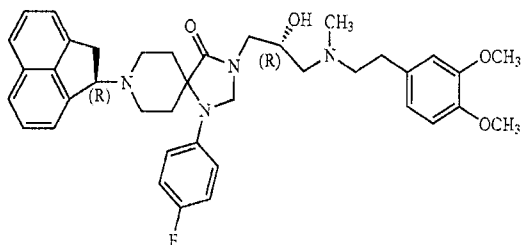
in mineral oil, 0.195 g, 4.856 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0° C. for 40 minutes and then warmed to room temperature. To the reaction mixture was then added (S)-epichlorhydrin (0.87 mL, 11.208 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (1.5% methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (300 MHz, CDCl₃) δ 7.70–7.65 (1H, m), 7.60 (1H, d, J=8.2 Hz), 7.54–7.49 (2H, m), 7.44 (1H, t), 7.26 (1H, d), 7.05–6.93 (4H, m), 4.95 (1H, dd, J=3.4 and 7.8 Hz), 4.77–4.74 (1H, m), 4.66–4.64 (1H, m), 4.0 (1H, d, J=12.5 Hz), 3.56–3.32 (2H, m), 3.21–3.03 (4H, m), 2.83–2.80 (2H, m), 2.59–2.55 (1H, m), 2.46–2.30 (2H, m), 2.27–2.21 (1H, m), 1.77–1.60 (2H, m)

MS (ES⁺) m/z 458.3 (M+H)⁺.

EXAMPLE 12

(R)-8-Acenaphthen-1-yl-3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-amino}-(R)-2-hydroxy-propyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #339



8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (1.5 g, 3.28 mmol), [2-(3,4-dimethoxy-phenyl)-ethyl]-methylamine hydrochloride (2.3 g, 9.92 mmol) and N,N-diisopropylethylamine (5 mL, 28.7 mmol) were dissolved in ethanol (40 mL). The reaction mixture was heated at 80° C. for 18 hours, then cooled to room temperature and the solvent evaporated in vacuo to yield an oil. The oil was partitioned with water and ethyl acetate. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (2% [methanol in ammonia 2.0M]/dichloromethane) to yield the title compound as a foam.

Chiral resolution: Diastereoisomers were separated using a CHIRALCEL OD-H column with methanol as mobile phase and generated the two pure diastereoisomers R, R and R, S.

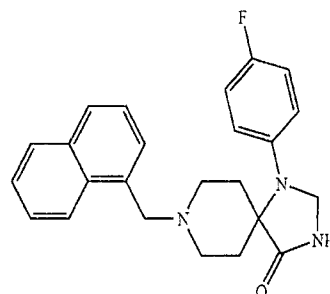
¹H NMR (300 MHz, CDCl₃) δ 7.69–7.65 (1H, m), 7.60 (1H, d, J=8.2 Hz), 7.54–7.50 (2H, m), 7.44 (1H, t), 7.27–7.25 (1H, m), 7.04–6.92 (4H, m), 6.77–6.64 (3H, m), 4.97–4.94 (1H, m), 4.79–4.71 (2H, m), 3.82 (3H, s), 3.81 (3H, s), 3.58–3.51 (3H, m), 3.38–3.02 (5H, m), 2.84–2.80 (1H, m), 2.77–2.53 (4H, m), 2.49–2.26 (7H, m), 1.76–1.59 (2H, m)

MS (ES⁺) m/z 653.4 (M+H)⁺.

104

EXAMPLE 13

1-(4-Fluoro-phenyl)-8-naphthalen-1-ylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #507



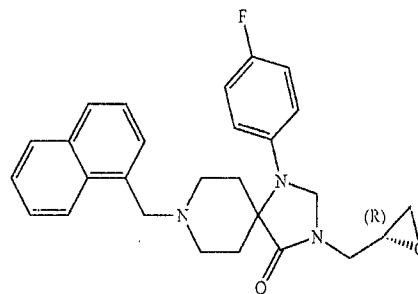
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1.0 g, 4.01 mmol) and naphthalene-1-carbaldehyde (0.75 g, 4.81 mmol) were dissolved in dry tetrahydrofuran (60 mL). To the reaction mixture was then added at 0° C. sodium triacetoxyborohydride (1.27 g, 6.01 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (3% methanol/dichloromethane) to yield the title compound as a solid.

¹H NMR (300 MHz, CDCl₃) δ 8.39–8.36 (1H, m), 7.87–7.75 (2H, m), 7.56–7.37 (4H, m), 6.99–6.85 (4H, m), 4.67 (2H, s), 3.97 (2H, s), 2.91–2.83 (4H, m), 2.42–2.31 (2H, m), 1.75–1.71 (2H, m)

MS (ES⁺) m/z 390.1 (M+H)⁺.

EXAMPLE 14

1-(4-Fluoro-phenyl)-8-naphthalen-1-ylmethyl-(R)-3-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #514



(R)-1-(4-Fluoro-phenyl)-8-naphthalen-1-ylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.218 g, 0.559 mmol) was dissolved in N,N-dimethylformamide (2.2 mL). To the reaction mixture was then added at 0° C. sodium hydride (60% in mineral oil, 30 mg, 0.727 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0° C. for 40 minutes. To the reaction mixture was then added (S)-epichlorhydrin (0.13 mL, 1.679 mmol) at 0° C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via

105

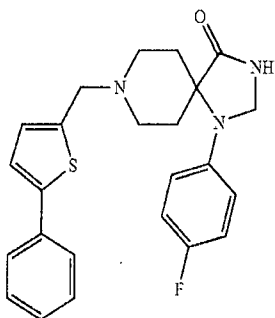
flash chromatography (2% methanol/dichloromethane) to yield the title compound as a solid.

^1H NMR (300 MHz, CDCl_3) δ 8.38–8.35 (1H, m), 7.87–7.75 (2H, m), 7.56–7.37 (4H, m), 6.99–6.86 (4H, m), 4.78–4.65 (2H, m), 4.08–3.97 (3H, m), 3.21–3.12 (2H, m), 2.95–2.82 (5H, m), 2.61–2.59 (1H, m), 2.40–2.30 (2H, m), 1.72–1.59 (2H, m)

MS (ES^+) m/z 446.3 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 15

1-(4-Fluoro-phenyl)-8-(5-phenyl-thien-2-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #546



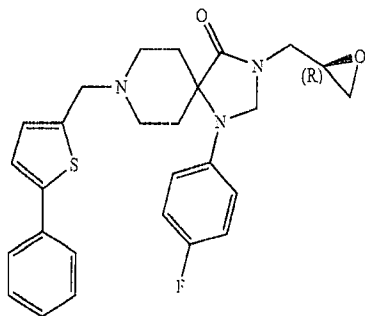
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.15 g, 0.601 mmol) and 5-phenyl-thienyl-2-carbaldehyde (0.136 g, 0.722 mmol) were dissolved in dry tetrahydrofuran (12 mL). To the reaction mixture was then added at 0° C. sodium triacetoxyborohydride (0.192 g, 0.902 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was partitioned with 1 N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 , filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/dichloromethane) to yield the title compound as a solid.

^1H NMR (300 MHz, CDCl_3) δ 7.59–7.56 (2H, m), 7.38–7.33 (2H, m), 7.27–7.22 (1H, m), 7.18–7.13 (1H, m), 7.05–6.92 (4H, m), 6.87 (1H, d, $J=3.6$ Hz), 6.26 (1H, br s), 4.67 (2H, s), 3.75 (2H, s), 2.87–2.78 (4H, m), 2.40–2.30 (2H, m), 1.76 (2H, d, $J=14.1$ Hz)

MS (ES^+) m/z 422.1 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 16

(R)-1-(4-Fluoro-phenyl)-3-oxiranylmethyl-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #541



106

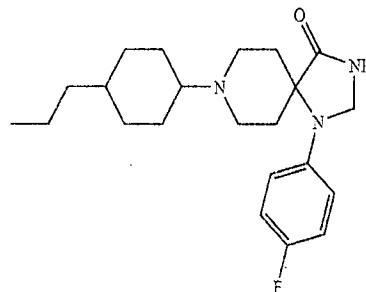
1-(4-Fluoro-phenyl)-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza spiro[4.5]decan-4-one (0.105 g, 0.249 mmol) was dissolved in N,N-dimethylformamide (2.5 mL). To the reaction mixture was then added at 0° C. sodium hydride (60% in mineral oil, 13 mg, 0.323 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0° C. for 40 minutes. To the reaction mixture was then added (S)-epichlorhydrin (0.058 mL, 0.747 mmol) at 0° C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 , filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/dichloromethane) to yield the title compound as a solid.

^1H NMR (300 MHz, CDCl_3) δ 7.59–7.55 (2H, m), 7.38–7.33 (2H, m), 7.27–7.22 (1H, m), 7.14 (1H, d, $J=3.6$ Hz), 7.05–6.92 (4H, m), 6.87 (1H, d, $J=3.5$ Hz), 4.77 (1H, d, $J=4.8$ Hz), 4.66 (1H, d, $J=4.8$ Hz), 4.06–3.99 (1H, m), 3.76 (2H, s), 3.20–3.13 (2H, m), 2.95–2.82 (3H, m), 2.60–2.58 (1H, m), 2.38–2.30 (2H, m), 1.75–1.67 (2H, m)

MS (ES^+) m/z 478.2 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 17

1-(4-Fluoro-phenyl)-8-(4-propyl-cyclohexyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #504



1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.25 g, 1.00 mmol) was dissolved in dry toluene (10 mL). To the reaction mixture was then added 4-propyl-cyclohexanone (0.14 g, 1.00 mmol), powder molecular sieve 4A (0.5 g) and the reaction mixture was refluxing for 18 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered through Celite. The Celite cake was washed with dry dichloromethane and the combined filtrate evaporated in vacuo to dryness. The residue was dissolved in dry tetrahydrofuran (4 mL) and dry methanol (0.5 mL). To the solution was then added sodium cyanoborohydride (21 mg), the pH of the solution was adjusted to pH 4 with a few drops of glacial acetic acid and the reaction mixture was stirred for 48 hours at room temperature under nitrogen atmosphere. The reaction mixture was partitioned with 1N NaOH and ethyl acetate. The organic layer was dried with Na_2SO_4 , filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (gradient 2–4% methanol/dichloromethane) to yield the title compound.

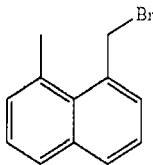
^1H NMR (300 MHz, CDCl_3) δ 7.02–6.93 (4H, m), 6.54 (1H, br d, $J=9.1$ Hz), 4.67 (2H, s), 3.05–2.70 (4H, m), 2.38–2.15 (3H, m), 1.9–1.11 (15H, m), 0.94–0.84 (3H, m)

MS (ES^+) m/z 374.0 ($\text{M}+\text{H}$) $^+$.

107

EXAMPLE 18

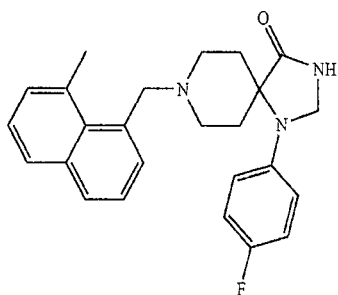
1-Bromomethyl-8-methyl-naphthalene



1,8-Dimethyl-naphthalene (1.30 g, 8.32 mmol) was dissolved in dry carbon tetrachloride (80 mL). To the reaction mixture was added N-bromosuccinimide (1.39 g, 7.82 mmol), dibenzoyl peroxide (6 mg, catalyst) and the reaction mixture was refluxing for 6 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, a precipitate formed on cooling and the precipitate was separated by filtration. The filtrate was evaporated in vacuo to yield the title compound as a solid which was used in further steps without additional purification.

EXAMPLE 19

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #547



1-Bromomethyl-8-methyl-naphthalene (1.72 g, 7.31 mmol) and 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1.29 g, 5.17 mmol) were dissolved in N,N-dimethylformamide (50 mL). Potassium carbonate (2.4 g, 15.52 mmol) and potassium iodide (0.02 g) were added and the reaction mixture was stirred at 30° C. under nitrogen atmosphere for 18 hours. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude solid. The crude solid was recrystallized from diethyl ether to yield the title compound as a solid.

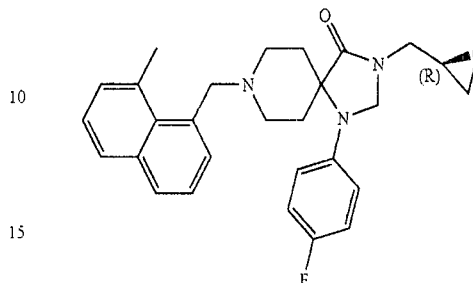
¹H NMR (300 MHz, CDCl₃) δ 7.79–7.76 (1H, m), 7.72–7.69 (1H, m), 7.39–7.30 (4H, m), 6.98–6.92 (2H, m), 6.87–6.82 (2H, m), 6.24 (1H, br s), 4.66 (2H, s), 4.01 (2H, s), 3.12 (3H, s), 2.86–2.78 (4H, m), 2.33–2.23 (2H, m), 1.72 (2H, d, J=14.1 Hz)

MS (ES⁺) m/z 404.2 (M+H)⁺.

108

EXAMPLE 20

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #553



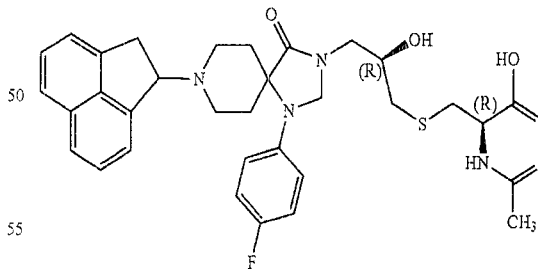
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.91 g, 2.25 mmol) was dissolved in N,N-dimethylformamide (10.5 mL). To the reaction mixture was then added at 0° C. sodium hydride (60% in mineral oil, 117 mg, 2.93 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0° C. for one hour, then warmed to room temperature. To the reaction mixture was then added (S)-epichlorohydrin (0.53 mL, 6.76 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (2.5% methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (300 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.39–7.30 (4H, m), 6.99–6.92 (2H, m), 6.88–6.83 (2H, m), 4.76 (1H, d, J=4.8 Hz), 4.64 (1H, d, J=4.8 Hz), 4.0 (2H, s), 3.21–3.11 (6H, m), 2.86–2.78 (5H, m), 2.60–2.58 (1H, m), 2.30–2.22 (2H, m), 1.70–1.62 (2H, m)

MS (ES⁺) m/z 460.2 (M+H)⁺.

EXAMPLE 21

3-{3-[8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(R)-hydroxypropylsulfanyl}-2-acetylamino-(R)-propionic acid Compound #100



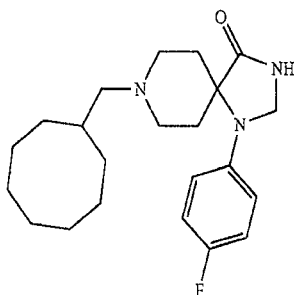
8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.022 g, 0.048 mmol) and N-acetyl-L-cysteine (0.03 g, 0.184 mmol) were dissolved in ethanol (1 mL). The reaction mixture was heated at 80° C. for 18 hours, then cooled to room temperature and the solvent evaporated in vacuo to yield an oil. The oil was partitioned with water and ethyl acetate. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via preparative TLC plate (10% methanol/dichloromethane) to yield the title compound as an oil.

US 7,081,463 B2

109

EXAMPLE 22

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compounds #582



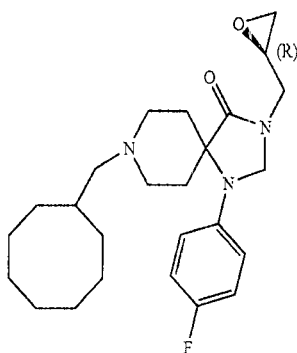
Cyclooctanecarbaldehyde (0.676 g, 4.8 mmol) synthesized according to the procedure described in Kawamoto, H. et. al. *Tetrahedron* 2001, 57, 981-986 was reacted with 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1 g, 4 mmol) in tetrahydrofuran (anhydrous, 100 mL), with the addition of sodium triacetoxymethylborohydride (1.2 g, 6 mmol) at 0° C. The reaction was then stirred overnight at room temperature. The organic layer was partitioned with 1 N sodium hydroxide, water and brine. The organic layer was dried with sodium sulfate and filtered to yield a clear residue. Purification of the residue by flash chromatography yielded the title compound as a white powder.

MS (electrospray)=374.1 (MH⁺)

¹H NMR (300 MHz, CDCl₃) δ 1.1-1.9 (m, 15H), 2.1 (d, 2H), 2.2-2.4 (m, 2H), 2.7 (d, 4H), 3.3 (d, 2H), 4.7 (s, 2H), 6.4 (s, 1H), 6.8-7.0 (m, 4H).

EXAMPLE 23

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-(R)-3-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #540



8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (4, 3 g, 8 mmol) was dissolved with NMP (150 mL) and stirred at 0° C. Sodium hydride (60% dispersion in oil, 0.75 g, 18.7 mmol) was added to the reaction mixture which was then stirred an additional 30 minutes at 0° C. S-(+)-epichlorohydrin (1.88 mL, 24 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was then partitioned with water and ethyl acetate. The organic was dried with sodium sulfate and filtered. The solvent was evaporated to yield the title compound as an oil.

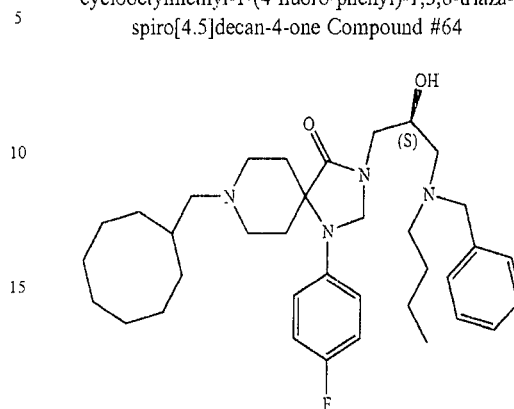
MS (electrospray)=430.5 (MH⁺)

¹H NMR (300 MHz, CDCl₃) δ 1.1-1.9 (m, 17H), 2.15 (d, 2H), 2.2-2.4 (m, 2H), 2.5-2.85 (m, 4H), 3.1 (m, 2H), 4.0 (m, 1H), 4.65 (d, 1H), 4.75 (d, 1H), 6.8-7.0 (m, 4H)

110

EXAMPLE 24

3-[3-(Benzyl-butyl-amino)-2-(S)-hydroxy-propyl]-8-cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #64



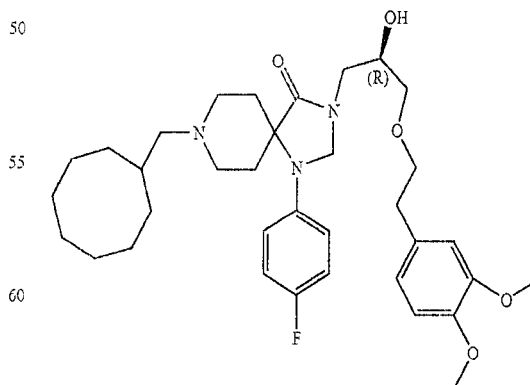
Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (3.4 g, 8 mmol) was dissolved in absolute ethanol (75 mL), mixed with N-butylbenzylamine (3.1 mL, 17.6 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by column chromatography (5% MeOH/CH₂Cl₂) to yield the free base as an oil. The oil (2.2 g, 3.7 mmol) was dissolved in diethyl ether (10 mL) and reacted with HCl (11 mL, [1 M in diethylether]) at 0° C. The resulting crystals were collected by filtration and recrystallized with ethanol to yield 1 g the title compound white powder.

MS (electrospray)=593.5 (MH⁺), 592.6

¹H NMR (300 MHz, CD₃OD) δ 1.1 (m, 3H), 1.3-1.9 (m, 15H), 2.1 (m, 2H), 2.4 (m, 2H), 2.9-3.6 (m, 14H), 3.65-3.8 (m, 2H), 4.2 (m, 1H), 4.3-4.3 (m, 3H), 4.8 (m, 2H), 7.0-7.2 (m, 4H), 7.4-7.7 (m, 5H)

EXAMPLE 25

8-Cyclooctylmethyl-3-{3-[2-(3,4-dimethoxy-phenyl)-ethoxy]-2-(R)-hydroxy-propyl}-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #105



3,4-Dimethoxyphenethylalcohol was dissolved in NMP (2 mL) and stirred for 30 min. NaH (60% dispersion in oil)

US 7,081,463 B2

111

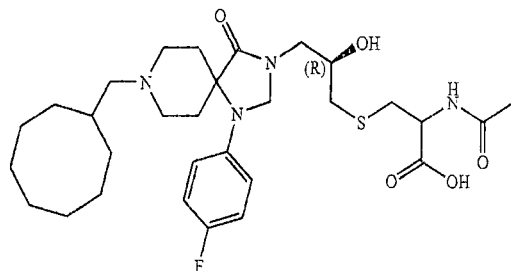
was added and the mixture was stirred for thirty minutes. 8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.2 g, 0.46 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was partitioned with saturated NaHCO₃ solution and ethyl acetate. The organic layer was dried with MgSO₄, filtered and the solvent evaporated in vacuo to yield crude product. Purification by reverse phase chromatography (AcCN/water) yielded the title compound as a trifluoroacetate salt as a solid.

MS (electrospray)=612.1 (MH⁺), 522.0, 402.2

¹H NMR (300 MHz, CD₃OD) δ 1.3–1.8 (m, 14H), 2.0–2.1 (m, 4H), 2.2–2.4 (m, 2H), 2.8 (t, 2H), 3.0 (d, 2H), 3.35–3.8 (m, 13H), 3.9 (m, 4H), 4.7 (m, 2H), 6.8 (m, 3H), 7.1 (m, 4H)

EXAMPLE 26

2-Acetylamino-3-{3-[8-cyclooctylmethyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(R)-hydroxy-propylsulfanyl}-propionic acid
Compound #100

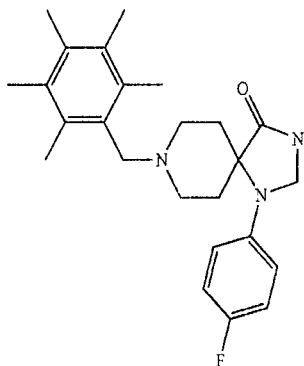


1-(4-fluorophenyl)-3R-oxaranyl-methyl-8-cyclooctylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.06 g, 0.14 mmol) was dissolved in absolute ethanol (1 mL), mixed with N-acetylcysteine (68 mg, 0.42 mmol) and heated to 70° C. overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (AcCN/water) to yield the title compounds as a trifluoroacetate salt as a solid.

MS (electrospray)=593.8 (MH⁺).

EXAMPLE 27

1-(4-Fluoro-phenyl)-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #583



Pentamethylbenzaldehyde (4 g, 23 mmol, commercially available) was reacted with 1-(4-Fluoro-phenyl)-1,3,8-

112

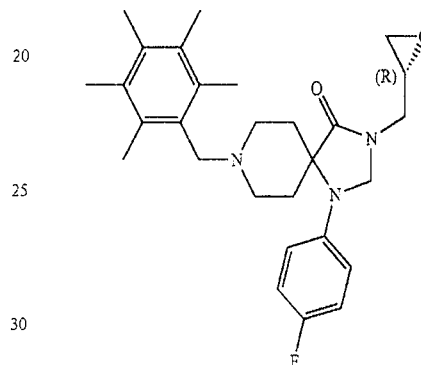
triaza-spiro[4.5]decan-4-one (5.5 g, 20 mmol) in tetrahydrofuran (anhydrous, 250 mL), with addition of sodium triacetoxyborohydride (8.2 g, 42 mmol) at 0° C. The reaction was then stirred overnight at room temperature. The organic layer was partitioned with 1 N sodium hydroxide, water and brine. The organic layer was dried with sodium sulfate and filtered to yield the title compound as a white powder.

MS (electrospray)=410.5 (MH⁺), 250.0

¹H NMR (300 MHz, DMSO-d₆) δ 1.6 (d, 2H), 2.2–2.3 (m, 17H), 2.6–2.8 (m, 4H), 3.55 (s, 2H), 4.5 (s, 2H), 6.8 (m, 2H), 7.1 (t, 2H), 8.65 (s, 1H).

EXAMPLE 28

1-(4-Fluoro-phenyl)-3R-oxiranylmethyl-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #584

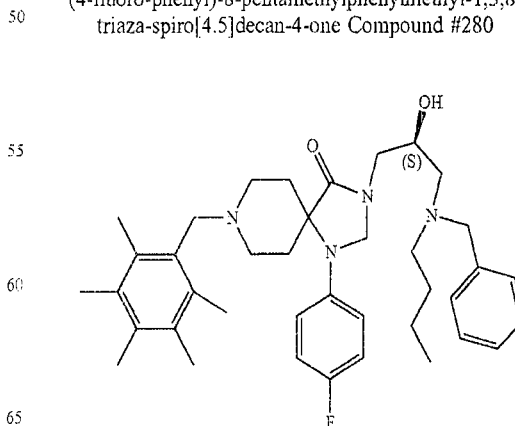


1-(4-Fluoro-phenyl)-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.6 g, 1.46 mmol) was dissolved with NMP (5 mL) and stirred at room temperature. Sodium hydride (60% dispersion in oil, 0.11 g, 1.6 mmol) was added and the mixture stirred an additional 30 minutes. S-(+)-epichlorohydrin (0.3 ml, 3.2 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was then partitioned with water and ethyl acetate. The organic was dried with sodium sulfate and filtered. The solvent was evaporated to yield the title compounds as an oil.

MS (electrospray)=466.1 (MH⁺)

EXAMPLE 29

3-[3-(Benzyl-butyl-amino)-2-(S)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #280



113

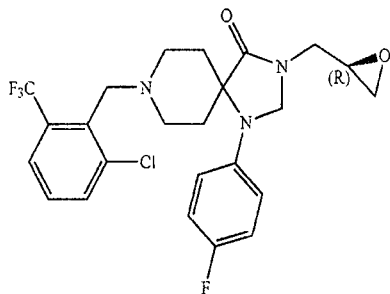
1-(4-Fluoro-phenyl)-3R-oxiranylmethyl-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.1 g, 0.21 mmol) was dissolved in absolute ethanol (75 mL), mixed with N-butylbenzylamine (0.1 mL, 0.6 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (AcCN/water) to yield the title compound as an oil.

MS (electrospray)=629.2 (MH⁺), 468.9, 315.3, 311.9, 161.1

¹H NMR (300 MHz, CD₃OD) δ 1.0 (m, 3H), 1.3 (m, 2H), 1.8 (m, 2H), 1.9 (m, 2H), 2.25 (d, 9H), 2.3 (s, 6H), 3.2 (m, 3H), 3.4 (m, 4H), 3.9 (m, 3H), 4.15 (m, 1H), 4.4 (m, 4H), 4.8 (m, 2H), 7.0 (m, 3H), 7.5 (m, 9H).

EXAMPLE 30

8-(2-Chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-3R-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #578

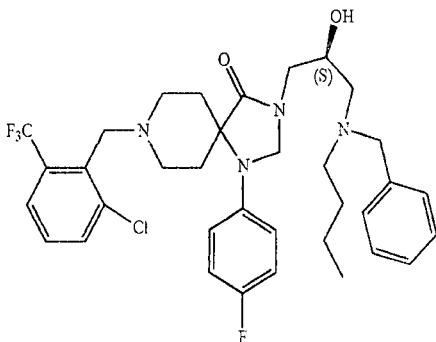


8-(2-Chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.3 g, 0.68 mmol) was dissolved with NMP (20 mL) and stirred at room temperature. Sodium hydride (60% dispersion in oil, 0.066 g, 0.95 mmol) was added and the mixture was stirred an additional 30 minutes. S-(+)-epichlorohydrin (0.14 mL, 1.5 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was then partitioned with water and ethyl acetate. The organic was dried with sodium sulfate and filtered. The solvent was evaporated to yield the title compound as an oil.

¹H NMR (300 MHz, CDCl₃) δ 1.6 (m, 2H), 2.3 (m, 2H), 2.7 (m, 2H), 2.9 (bt, 2H), 3.1 (m, 1H), 3.8 (s, 2H), 4.0 (d, 1H), 4.6 (d, 1H), 4.8 (d, 2H), 6.8 (m, 2H), 6.95 (m, 2H), 7.2 (t, 1H), 7.6 (t, 2H).

EXAMPLE 31

3-[3-(Benzyl-butyl-amino)-2-(S)-hydroxy-propyl]-8-(2-chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #456)



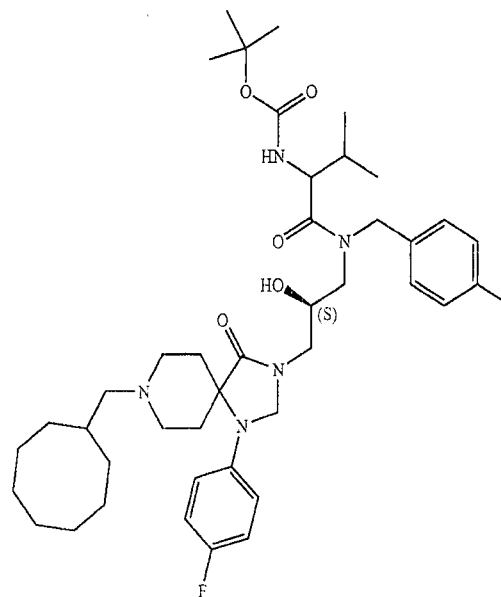
114

8-(2-Chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.1 mmol) was dissolved in absolute ethanol (0.5 mL), mixed with N-butylbenzylamine (0.05 mL, 0.4 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse column chromatography (AcCN/water) to yield the title compound as an oil.

MS (electrospray)=661.0 (MH⁺), 571.1, 331.4

EXAMPLE 32

{1-[[3-[8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(S)-hydroxy-propyl]-(4-methyl-benzyl)-carbamoyl]-2-methyl-propyl}-carbamic acid tert-butyl ester Compound #79



8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(4-methyl-benzylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.091 mmol) was dissolved in DMF (1 mL), mixed with BocD-Valine (0.02 g, 0.091 mmol), HBTU (0.035 g, 0.09 mmol) and diisopropylethylamine (0.1 mL) and stirred overnight at room temperature. The reaction mixture was partitioned with saturated NaHCO₃ and ethyl acetate. The organic layer dried with, MgSO₄, filtered and the solvent evaporated in vacuo to yield the title compound as an oil.

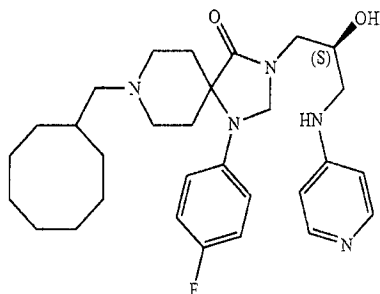
MS (electrospray)=751.5 (MH⁺), 749.8, 373.6, 372.8, 203.1, 171.1

US 7,081,463 B2

115

EXAMPLE 33

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-[2-(S)-hydroxy-3-(pyridin-4-ylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #36

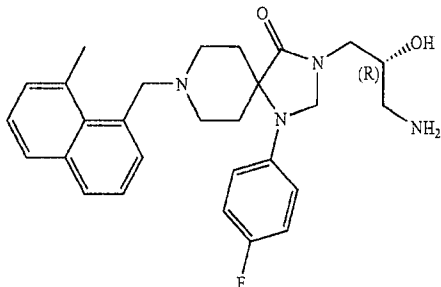


Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.5 g, 1.16 mmol) was dissolved in absolute ethanol (1 mL), mixed with 4-Aminopyridine (0.5 mL, 5.3 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase column chromatography (Acetonitrile/water) to yield the title compound as an oil.

¹H NMR (300 MHz, CD₃OD) δ 1.35 (m, 2H), 1.5–1.7 (m, 13H), 1.9 (s, 9H), 1.95 (m, 1H), 2.4 (m, 2H), 3.1 (d, 2H), 3.2 (m, 2H), 3.4 (m, 2H), 3.55 (d, 2H), 4.0 (m, 1H), 4.15 (m, 1H), 4.3 (m, 1H), 6.8 (d, 2H), 7.1 (m, 4H), 8.1 (d, 2H).

EXAMPLE 34

3-[3-Amino-2-(R)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #438



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.06 g, 0.13 mmol) was dissolved in ethyl alcohol (2 mL) and methyl alcohol (0.4 mL). To the solution was then added concentrated ammonium hydroxide (1 mL) and the reaction mixture was stirred at 40° C. for two hours in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

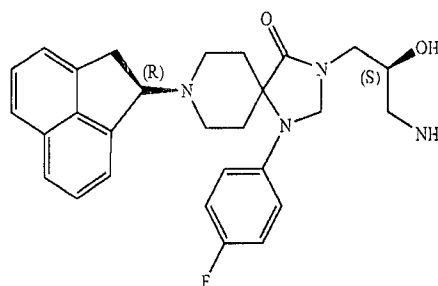
¹H NMR (400 MHz, CDCl₃) δ 7.77–7.75 (1H, m), 7.71–7.68 (1H, m), 7.37–7.30 (4H, m), 6.97–6.91 (2H, m), 6.87–6.83 (2H, m), 4.74 (2H, s), 4.0 (2H, s), 3.79–3.74 (1H,

116

EXAMPLE 35

m), 3.57–3.52 (1H, m), 3.41–3.36 (1H, m), 3.11 (3H, s), 2.91–2.74 (4H, m), 2.66–2.61 (1H, m), 2.30–2.23 (2H, m), 1.66 (2H, d, J=13.7 Hz)
MS (ES⁺) m/z 477.1 (M+H)⁺.

(R)-8-Acenaphthen-1-yl-3-(3-amino-2-hydroxy-(S)-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #424

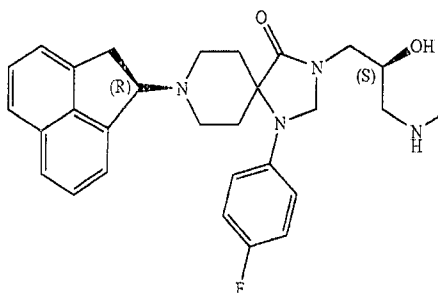


(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.514 g, 1.123 mmol) was dissolved in ethyl alcohol (16 mL). To the solution was then added concentrated ammonium hydroxide (8 mL) and the reaction mixture was stirred at 40° C. for two hours and a half in a pressure flask. The solvent was then evaporated in vacuo to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.68–7.65 (1H, m), 7.60 (1H, d, J=8.2 Hz), 7.52–7.49 (2H, m), 7.43 (1H, t), 7.26 (1H, d), 7.03–6.94 (4H, m), 4.97–4.94 (1H, m), 4.76–4.72 (2H, m), 3.74 (1H, br s), 3.55–3.48 (2H, m), 3.38–3.32 (2H, m), 3.16–3.03 (2H, m), 2.88–2.82 (2H, m), 2.59 (1H, br s), 2.44–2.41 (2H, m), 2.31–2.24 (1H, m), 1.76–1.62 (2H, m)
MS (ES⁺) m/z 475.2 (M+H)⁺.

EXAMPLE 36

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(2-hydroxy-3-methylamino-(S)-propyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #437



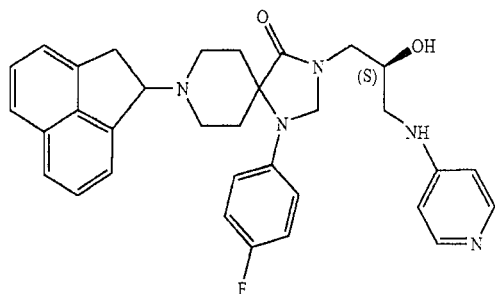
(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.045 g, 0.098 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a solution of 2.0M methylamine in THF (1 mL) and the reaction mixture was stirred at 40° C. for two hours and a half in a pressure flask. The solvent was then evaporated in vacuo to yield the title compound as a foam.

117

¹H NMR (400 MHz, CDCl₃) δ 7.68–7.64 (1H, m), 7.59 (1H, d, J=8.2 Hz), 7.53–7.49 (2H, m), 7.45 (1H, t), 7.26–7.24 (1H, m), 7.03–6.94 (4H, m), 4.96–4.93 (1H, m), 4.78–4.73 (2H, m), 3.86–3.83 (1H, m), 3.55–3.47 (2H, m), 3.37–3.30 (2H, m), 3.16–2.99 (2H, m), 2.87–2.79 (2H, m), 2.70–2.66 (1H, m), 2.52–2.23 (6H, m), 1.75–1.61 (2H, m). MS (ES⁺) m/z 489.3 (M+H)⁺.

EXAMPLE 37

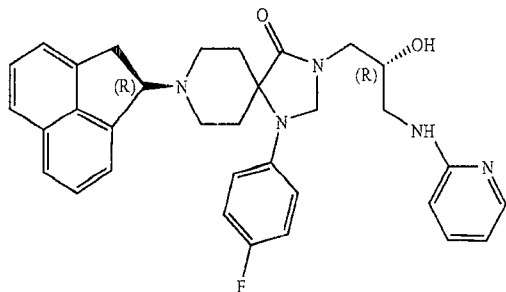
8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(pyridin-4-ylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #327



8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(R)oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.100 g, 0.21 mmol) was dissolved in absolute ethyl alcohol (0.5 mL), mixed with 4-aminopyridine (0.2 mL) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (MeCN/water) to yield the title compound as an oil.

EXAMPLE 38

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(pyridin-2-ylamino)-(R)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #421



Sodium amide (0.0085 g, 0.21 mmol) and 2-aminopyridine (0.0165 g, 0.17 mmol) were suspended in toluene (0.25

118

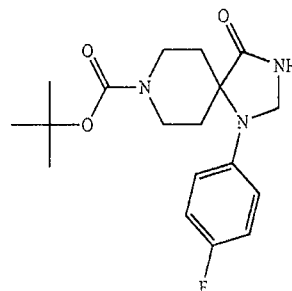
mL) and benzene (0.15 mL). To the reaction mixture was then added (R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(S)oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.100 g, 0.21 mmol). The mixture was refluxed overnight under nitrogen, cooled down to room temperature and partitioned with brine and dichloromethane. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (3.25% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as an oil.

¹H NMR (300 MHz, CDCl₃) δ 7.98–7.96 (1H, m), 7.69–7.65 (1H, m), 7.60 (1H, d, J=8.2 Hz), 7.53–7.51 (2H, m), 7.47–7.40 (1H, m), 7.28–7.26 (1H, m), 7.03–6.92 (4H, m), 6.66–6.47 (3H, m), 5.08–5.04 (1H, m), 4.98–4.94 (1H, m), 4.79–4.73 (2H, m), 4.0–3.94 (1H, m), 3.72–3.61 (2H, m), 3.57–3.49 (1H, m), 3.40–3.28 (2H, m), 3.14–3.02 (2H, m), 2.85–2.81 (1H, m), 2.44–2.26 (3H, m), 1.74–1.25 (2H, m).

MS (ES⁺) m/z 552.3 (M+H)⁺.

EXAMPLE 39

1-(4-Fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester Compound #535



Di-tert-butyl dicarbonate (2.2 g, 10.0 mmol) and 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (2.5 g, 10.0 mmol) were dissolved in dioxane (50 mL) and water (100 mL). Sodium hydrogen carbonate (1.7 g, 20 mmol) was then added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours. The reaction mixture was concentrated in vacuo and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a solid. Recrystallization from hot ethyl acetate yielded the title compound as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.25 (1H, br s), 7.0–6.95 (2H, m), 6.82–6.77 (2H, m), 4.71 (2H, s), 4.08–3.8 (2H, m), 3.65–3.40 (2H, m), 2.35–2.15 (2H, m), 1.8–1.65 (2H, m), 1.48 (9H, s).

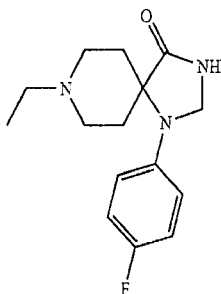
MS (ES⁺) m/z 372.1 (MNa)⁺.

US 7,081,463 B2

119

EXAMPLE 40

8-Ethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]
decan-4-one Compound #536



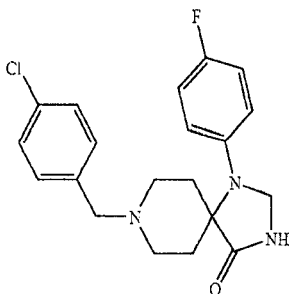
2-iodoethane (0.47 g, 3.0 mmol) and 1-(4-fluoro-phenyl)-
1,3,8-triaza-spiro[4.5]decan-4-one (0.6 g, 2.4 mmol) were
dissolved in acetonitrile (15 mL). Potassium carbonate (0.66
g, 4.8 mmol) was then added and the reaction mixture was
stirred at room temperature under nitrogen atmosphere for
18 hours. The reaction mixture was partitioned with water
and diethyl ether. The organic layer was washed with brine,
dried with Na₂SO₄, filtered and the solvent evaporated in
vacuo to yield a crude oil. The crude oil was purified via
flash chromatography (30–50% ethyl acetate/hexane) to
yield the title compound as an oil.

¹H NMR (300 MHz, CDCl₃) δ 7.03–6.93 (4H, m), 6.46
(1H, br s), 4.67 (2H, s), 2.82–2.69 (4H, m), 2.48 (2H, q),
2.31–2.21 (2H, m), 1.81–1.76 (2H, m), 1.08 (3H, t)

MS (ES⁺) m/z 278.2 (M+H)⁺.

EXAMPLE 41

8-(4-Chloro-benzyl)-1-(4-fluoro-phenyl)-1,3,8-
triaza-spiro[4.5]decan-4-one Compound #508



120

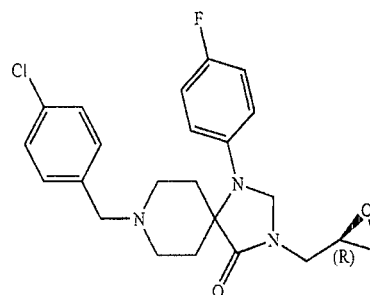
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one
(3.0 g, 12.03 mmol) and 4-chloro-benzaldehyde (2.03 g,
14.44 mmol) were dissolved in dry tetrahydrofuran (120
mL). To the reaction mixture was then added at 0° C. sodium
triacetoxyborohydride (3.82 g, 18.05 mmol) under nitrogen
atmosphere and the reaction mixture was stirred at room
temperature for 18 hours. The reaction mixture was then
partitioned with 1 N NaOH and ethyl acetate. The organic
layer was washed with brine, dried with Na₂SO₄, filtered
and the solvent evaporated in vacuo to yield a crude oil. The
crude oil was purified via flash chromatography (3.5%
methanol/dichloromethane) to yield the title compound as a
white foam.

¹H NMR (300 MHz, CDCl₃) δ 7.30–7.15 (4H, m),
7.01–6.87 (4H, m), 4.63 (2H, s), 3.47 (2H, s), 2.78–2.65
(4H, m), 2.31–2.0 (2H, m), 1.73–1.68 (2H, m)

MS (ES⁺) m/z 374.1 (M+H)⁺.

EXAMPLE 42

8-(4-Chloro-benzyl)-1-(4-fluoro-phenyl)-3-(R)-ox-
iranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #513



8-(4-Chloro-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-
spiro[4.5]decan-4-one (0.220 g, 0.588 mmol) was dissolved
in N,N-dimethylformamide (2.2 mL). To the reaction mix-
ture was then added at 0° C. sodium hydride (60% in mineral
oil, 31 mg, 0.765 mmol) under nitrogen atmosphere and the
reaction mixture was stirred at 0° C. for 40 minutes. To the
reaction mixture was then added (S)-epichlorhydrin (0.14
mL, 1.765 mmol) at 0° C. The reaction mixture was stirred
at room temperature under nitrogen atmosphere for 18 hours
and partitioned with water and ethyl acetate. The organic
layer was washed with brine, dried with Na₂SO₄, filtered
and the solvent evaporated in vacuo to yield a crude oil. The
crude oil was purified via flash chromatography (2% metha-
nol/dichloromethane) to yield the title compound as a foam.

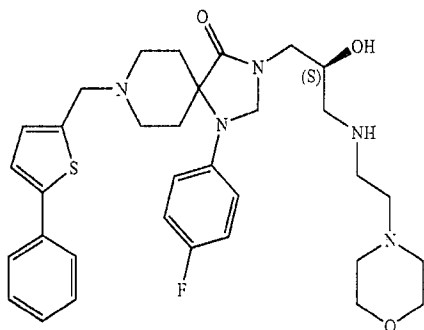
¹H NMR (300 MHz, CDCl₃) δ 7.32–7.26 (4H, m),
7.04–6.91 (4H, m), 4.77 (1H, d, J=4.9 Hz), 4.66 (1H, d,
J=4.9 Hz), 4.06–3.99 (1H, m), 3.52 (3H, s), 3.20–3.14 (2H,
m), 2.85–2.68 (5H, m), 2.60–2.58 (1H, m), 2.33–2.23 (2H,
m), 1.73–1.60 (2H, m)

MS (ES⁺) m/z 430.2 (M+H)⁺.

121

EXAMPLE 43

1-(4-Fluoro-phenyl)-3-(S)-[2-hydroxy-3-(2-morpholin-4-yl-ethylamino)-propyl]-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #293



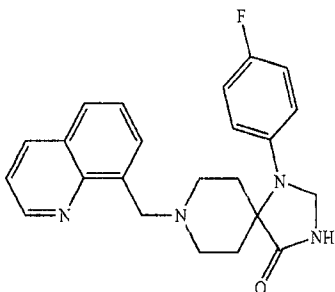
(R)-1-(4-Fluoro-phenyl)-3-oxiranylmethyl-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.041 mmol) was dissolved in absolute ethanol (1 mL), mixed with 2-morpholin-4-yl-ethylamine (16.3 mg, 0.125 mmol) and heated under stirring at 70° C. overnight. The solvent was evaporated and the resulting residue was purified via flash chromatography (9% methanol/dichloromethane) to yield the title compound as an oil.

¹H NMR (300 MHz, CDCl₃) δ 7.59–7.56 (2H, m), 7.38–7.33 (2H, m), 7.28–7.25 (2H, m), 7.14 (1H, d, J=3.6 Hz), 7.04–6.91 (3H, m), 6.87 (1H, d, J=3.5 Hz), 4.80–4.76 (2H, m), 3.86–3.69 (6H, m), 3.61–3.55 (1H, m), 3.36–3.29 (1H, m), 2.85–2.71 (7H, m), 2.58–2.32 (10H, m), 1.72 (2H, d, J=13.7 Hz)

MS (ES⁺) m/z 608.3 (M+H)⁺

EXAMPLE 44

1-(4-Fluoro-phenyl)-8-quinolin-8-ylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #522



1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.15 g, 0.601 mmol) and quinoline-8-carbaldehyde (0.113 g, 0.722 mmol) were dissolved in dry tetrahydrofuran (12

122

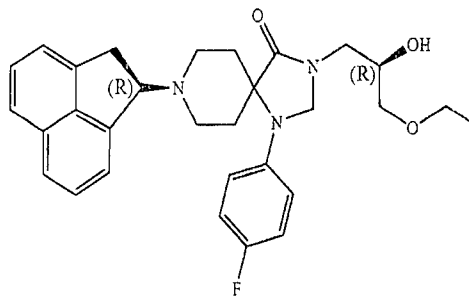
mL). To the reaction mixture was then added at 0° C. sodium triacetoxyborohydride (0.192 g, 0.902 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5% methanol/dichloromethane) to yield the title compound as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.93–8.91 (1H, m), 8.14 (1H, d, J=8.3 Hz), 7.89 (1H, br s), 7.71 (1H, m), 7.55 (1H, t, J=7.7 Hz), 7.41–7.38 (1H, m), 7.05–7.01 (4H, m), 6.79 (1H, br s), 4.69 (2H, s), 4.35 (2H, s), 3.01–2.90 (4H, m), 2.41 (2H, br s), 1.80 (2H, d, J=13.8 Hz)

MS (ES⁺) m/z 391.0 (M+H)⁺

EXAMPLE 45

(R)-8-Acenaphthen-1-yl-3-(R)-(3-ethoxy-2-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #571



(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(R)oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.084 g, 0.183 mmol) was dissolved in ethanol (4 mL). The reaction mixture was heated at 80° C. for 18 hours, then cooled to room temperature and the solvent evaporated in vacuo to yield an oil. The oil was partitioned with water and ethyl acetate. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (4% [methanol in ammonia 2.0M]/dichloromethane) to yield the title compound as an oil.

¹H NMR (300 MHz, CDCl₃) δ 7.69–7.66 (1H, m), 7.61 (1H, d, J=8.2 Hz), 7.54–7.50 (2H, m), 7.44 (1H, t), 7.27–7.25 (1H, m), 7.05–6.90 (4H, m), 4.98–4.90 (1H, m), 4.77–4.71 (2H, m), 4.03–3.98 (1H, m), 3.57–3.31 (8H, m), 3.16–3.01 (3H, m), 2.88–2.85 (1H, m), 2.43 (2H, br s), 2.32–2.24 (1H, m), 1.77–1.62 (2H, m), 1.18 (3H, t);

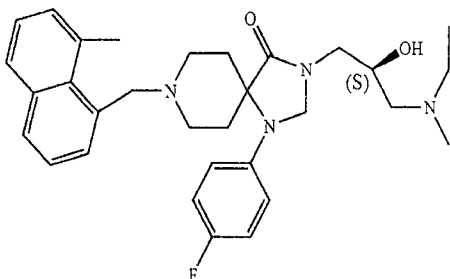
MS (ES⁺) m/z 504.3 (M+H)⁺

US 7,081,463 B2

123

EXAMPLE 46

3-[3-(Ethyl-methyl-amino)-2-hydroxy-(S)-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #440



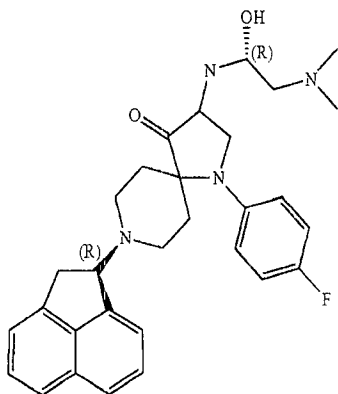
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.043 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added N-methylethylamine (0.2 mL) and the reaction mixture was stirred at 40° C. for 3 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as an oil.

¹H NMR (400 MHz, CDCl₃) δ 7.77–7.75 (1H, m), 7.71–7.68 (1H, m), 7.38–7.30 (4H, m), 6.96–6.91 (2H, m), 6.88–6.84 (2H, m), 4.82–4.75 (2H, m), 4.08–3.98 (3H, m), 3.61–3.57 (1H, m), 3.34–3.29 (1H, m), 3.11 (3H, s), 2.83–2.54 (8H, m), 2.44 (3H, s), 2.32–2.23 (2H, m), 1.68–1.63 (2H, m); 1.15 (3H, t, J=7.2 Hz)

MS (ES⁺) m/z 519.3 (M+H)⁺.

EXAMPLE 47

(R)-Acenaphthen-1-yl-3-(3-dimethylamino-2-hydroxy-(R)-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #423



124

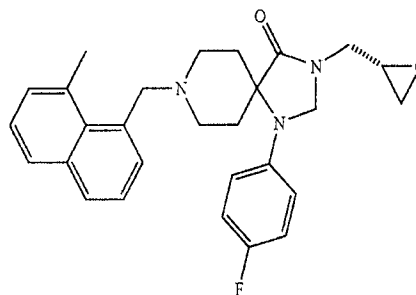
(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.057 g, 0.124 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a solution of 2.0M dimethylamine in THF (1 mL) and the reaction mixture was stirred at 40° C. for 2.5 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.68–7.65 (1H, m), 7.59 (1H, d, J=8.2 Hz), 7.52–7.49 (2H, m), 7.44 (1H, t), 7.26–7.25 (1H, m), 7.03–6.94 (4H, m), 4.97–4.94 (1H, m), 4.83–4.80 (2H, m), 4.77–4.75 (1H, m), 3.87–3.81 (1H, m), 3.60–3.03 (7H, m), 2.85–2.82 (1H, m), 2.49–2.42 (2H, m), 2.32–2.24 (8H, m), 1.75–1.62 (2H, m)

MS (ES⁺) m/z 503.3 (M+H)⁺.

EXAMPLE 48

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #550



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (2.0 g, 4.95 mmol) was dissolved in N,N-dimethylformamide (25.0 mL). To the reaction mixture was then added at 0° C. sodium hydride (60% in mineral oil, 238 mg, 5.94 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0° C. for one hour. To the reaction mixture was then added at 0° C. (2R)-(-)-glycidyl-3-nitrobenzenesulfonate (1.54 g, 5.94 mmol). The reaction mixture was stirred at 0° C. for one hour, then at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (2.5% methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (300 MHz, CDCl₃) δ 7.78–7.76 (1H, m), 7.73–7.69 (1H, m), 7.38–7.31 (4H, m), 6.99–6.91 (2H, m), 6.89–6.84 (2H, m), 4.76 (1H, d, J=4.8 Hz), 4.65 (1H, d, J=4.8 Hz), 4.01 (2H, s), 3.20–3.11 (6H, m), 2.86–2.77 (5H, m), 2.61–2.59 (1H, m), 2.31–2.21 (2H, m), 1.69–1.63 (2H, m)

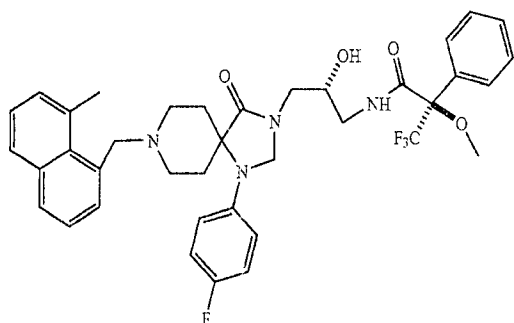
MS (ES⁺) m/z 460.2 (M+H)⁺.

US 7,081,463 B2

125

EXAMPLE 49

3,3,3-Trifluoro-N-{3-[1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-4-oxo-1,3,8-triaza-spiro[4.5]decan-3-yl]-2-(R)-hydroxy-propyl}-2-methoxy-2-phenyl-(R)-propionamide Compound #615



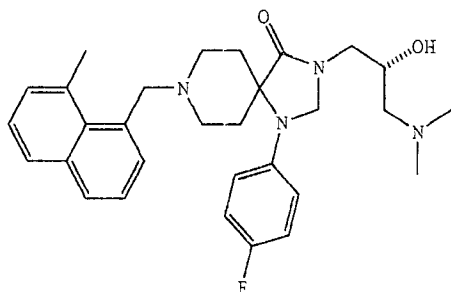
3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.0118 g, 0.024 mmol) was dissolved in dichloromethane (1.0 mL) and pyridine (0.15 mL). To the reaction mixture was then added at 0° C. (S)-(+)- α -methoxy- α -(trifluoro methyl)phenyl acetyl chloride (8.7 mg, 0.034 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0° C. for one hour, then the solvent was evaporated in vacuo to yield a crude foam. The crude foam was dissolved in ethyl acetate and successively washed twice with aqueous 0.5N HCl, twice with aqueous NaHCO₃, brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a white foam.

¹H NMR (300 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.64–7.61 (1H, m), 7.56–7.54 (2H, m), 7.42–7.40 (3H, m), 7.39–7.30 (3H, m), 6.97–6.93 (2H, m), 6.87–6.83 (2H, m), 4.70 (1H, d, J=4.9 Hz), 4.64 (1H, d, J=4.9 Hz), 3.99 (3H, s), 4.01 (1H, s), 3.60–3.54 (1H, m), 3.45–3.32 (5H, m), 3.1 (3H, s), 2.82–2.74 (4H, m), 2.24–2.20 (2H, m), 1.70–1.63 (4H, m).

MS (ES⁺) m/z 693.0 (M+H)⁺.

EXAMPLE 50

3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #441



126

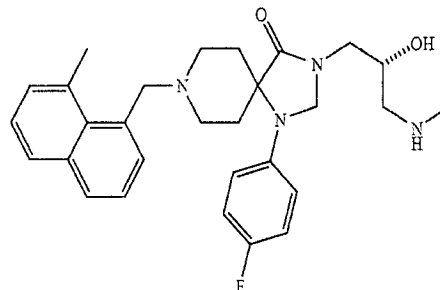
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.07 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a 2.0M solution of dimethylamine in methanol (1.0 mL, 2.0 mmol) and the reaction mixture was stirred at 45° C. for 3 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.38–7.31 (4H, m), 6.96–6.91 (2H, m), 6.88–6.84 (2H, m), 4.80 (1H, d, J=5.1 Hz), 4.77 (1H, d, J=5.1 Hz), 4.01 (2H, m), 3.95–3.87 (1H, m), 3.62–3.58 (1H, m), 3.31–3.26 (1H, m), 3.11 (3H, s), 2.86–2.78 (6H, m), 2.36–2.22 (9H, m), 1.68–1.63 (2H, m).

MS (ES⁺) m/z 505.4 (M+H)⁺.

EXAMPLE 51

1-(4-Fluoro-phenyl)-3-(2-(R)-hydroxy-3-methylamino-propyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #660



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.109 mmol) was dissolved in methanol (3 mL). To the solution was then added a 2.0M solution of methylamine in methanol (1.0 mL, 2.0 mmol) and the reaction mixture was stirred at 40° C. for 3 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

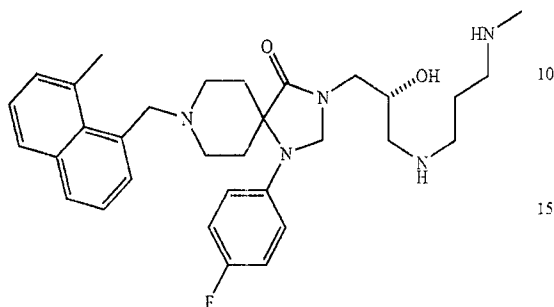
¹H NMR (400 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.38–7.31 (4H, m), 6.96–6.91 (2H, m), 6.88–6.84 (2H, m), 4.80 (1H, d, J=5.1 Hz), 4.77 (1H, d, J=5.1 Hz), 4.00 (2H, m), 3.97–3.86 (1H, m), 3.58–3.53 (1H, m), 3.43–3.35 (1H, m), 3.12 (3H, s), 2.84–2.69 (7H, m), 2.56–2.49 (1H, m), 2.44 (3H, s), 2.31–2.24 (2H, m), 1.67–1.64 (2H, m).

MS (ES⁺) m/z 491.1 (M+H)⁺.

127

EXAMPLE 52

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #656



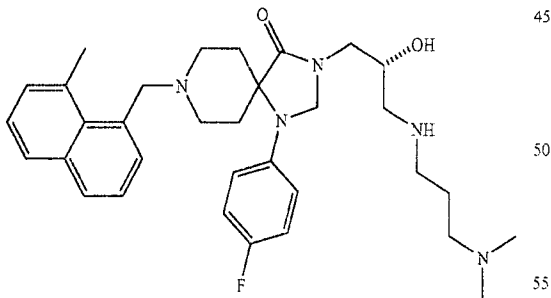
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.07 mmol) was dissolved in methanol (4 mL). To the solution was then added N-methyl-1,3-propanediamine (0.027 g, 0.35 mmol) and the reaction mixture was stirred at 45° C. for 12 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.38–7.30 (4H, m), 6.95–6.91 (2H, m), 6.87–6.84 (2H, m), 4.80 (1H, d, J=5.05 Hz), 4.77 (1H, d, J=5.05 Hz), 4.00 (2H, s), 3.96–3.89 (1H, m), 3.58–3.54 (1H, m), 3.32–3.30 (1H, m), 3.12 (3H, s), 2.85–2.77 (6H, m), 2.65–2.58 (1H, m), 2.49–2.12 (10H, m), 1.68–1.63 (4H, m)

MS (ES⁺) m/z 548.3 (M+H)⁺.

EXAMPLE 53

3-[3-(3-Dimethylamino-propylamino)-2-(R)-hydroxy-Propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #666



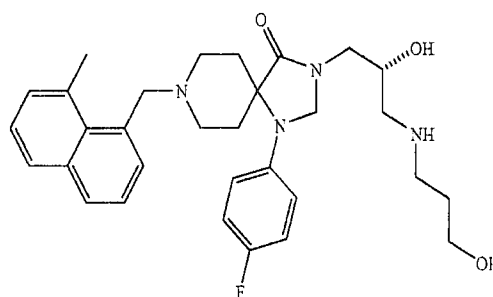
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.037 g, 0.07 mmol) was dissolved in ethanol (2 mL). To the solution was then added dimethylaminopropylamine (0.03 g, 0.3 mmol) and the reaction mixture was stirred at 45° C. for 12 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

128

¹H NMR (300 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.38–7.30 (4H, m), 6.97–6.90 (2H, m), 6.87–6.82 (2H, m), 4.78–4.73 (2H, m), 4.00 (2H, s), 3.96–3.82 (1H, m), 3.59–3.53 (1H, m), 3.37–3.30 (1H, m), 3.12 (3H, s), 2.86–2.50 (9H, m), 2.35–2.11 (11H, m), 1.68–1.59 (4H, m)
MS (ES⁺) m/z 562.2 (M+H)⁺.

EXAMPLE 54

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxy-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #651



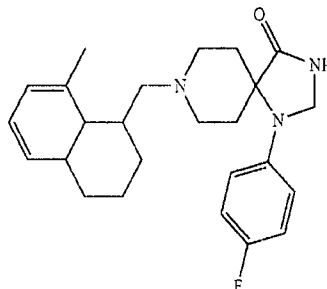
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (1.16 g, 2.5 mmol) was dissolved in methanol (20 mL). To the solution was then added 3-amino-1-propanol (0.375 g, 5.0 mmol) and the reaction mixture was stirred at 40° C. for 12 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (300 MHz, CDCl₃) δ 7.78–7.75 (1H, m), 7.71–7.68 (1H, m), 7.38–7.30 (4H, m), 6.97–6.90 (2H, m), 6.87–6.82 (2H, m), 4.74–4.70 (2H, m), 3.99 (2H, s), 3.96–3.90 (1H, m), 3.81–3.77 (2H, m), 3.47–3.42 (3H, m), 3.11 (3H, s), 2.91–2.56 (10H, m), 2.30–2.20 (2H, m), 1.76–1.63 (4H, m)

MS (ES⁺) m/z 535.2 (M+H)⁺.

EXAMPLE 55

11-(4-Fluoro-phenyl)-8-(8-methyl-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #728



Step A:

8-Methyl-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid (*J. Org. Chem.* 1982, 47, 2590–2593) (0.066 g, 0.34 mmol) was dissolved in tetrahydrofuran (3 mL). To the solution was then added at 0° C. a 1.0M solution of borane-methyl sulfide complex in dichloromethane (0.7 mL, 0.69 mmol). The reaction mixture was stirred at room temperature for 15 minutes, refluxed for 2 hrs, then cooled down to 0° C. and quenched with methanol. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was partitioned with water and diethyl ether. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield crude (8-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-methanol as an oil which was used directly to the next step.

¹H NMR (400 MHz, CDCl₃) δ 7.05–6.92 (3H, m), 3.70–3.59 (2H, m), 3.15–3.10 (1H, m), 2.83–2.71 (2H, m), 2.34 (3H, s), 2.21–2.16 (1H, m), 1.95–1.83 (1H, m), 1.79.1.67 (2H, m), 1.52 (1H, br s)

Step B:

(8-Methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-methanol (0.03 g, 0.17 mmol) was dissolved in dichloromethane (0.5 mL). To the solution was then added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3 (1H)-one, also known as Dess-Martin periodinane (0.087 g, 0.20 mmol). The reaction mixture was stirred for 2 hrs then partitioned with an aqueous saturated solution of thiosulfate and dichloromethane. The organic layer was washed with an aqueous saturated solution of thiosulfate, an aqueous saturated solution of sodium bicarbonate, brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield 8-methyl-1,2,3,4-tetrahydro-naphthalene-1-carbaldehyde as a solid.

¹H NMR (400 MHz, CDCl₃) δ 9.66 (1H, d, J=1.8 Hz), 7.13–6.99 (3H, m), 3.74–3.72 (1H, m), 2.81–2.77 (2H, m), 2.37–2.31 (1H, m), 2.2 (3H, s), 1.95–1.61 (3H, m).

Step C:

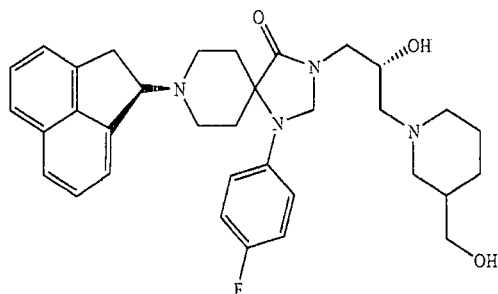
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.14 mmol) and 8-methyl-1,2,3,4-tetrahydro-naphthalene-1-carbaldehyde (0.03 g, 0.17 mmol) were dissolved in dry tetrahydrofuran (2 mL) and dry dichloromethane (0.5 mL). To the reaction mixture was then added at 0° C. sodium triacetoxyborohydride (0.045 g, 0.21 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (5% methanol/dichloromethane) to yield the title compound as an oil.

¹H NMR (400 MHz, CDCl₃) δ 7.06–6.90 (7H, m), 6.56 (1H, br s), 4.68 (2H, s), 3.12–2.33 (12H, m), 1.91–1.53 (6H, m), 1.25–1.21 (2H, m)

MS (ES⁺) m/z 408.1 (M+H)⁺.

EXAMPLE 56

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-(R)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #695



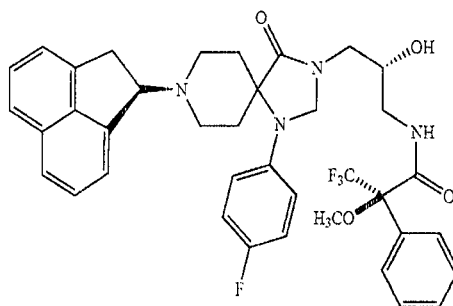
(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.04 mmol) was dissolved in ethyl alcohol (1.5 mL). To the solution was then added 3-piperidinemethanol (0.01 g, 0.08 mmol) and the reaction mixture was stirred at 60° C. for 12 hrs in a pressure flask. The solvent was evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.69–7.49 (4H, m), 7.46–7.41 (1H, m), 7.26–7.25 (1H, m), 7.04–6.95 (4H, m), 4.97–4.94 (1H, m), 4.81–4.74 (2H, m), 3.97–3.90 (1H, m), 3.58–1.6 (27H, m)

MS (ES⁺) m/z 573.3 (M+H)⁺.

EXAMPLE 57

N-{3-[(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-hydroxy-(R)-propyl}-3,3,3-trifluoro-2-methoxy-2-phenyl-(R)-propionamide Compound #645



(R)-8-Acenaphthen-1-yl-3-(3-amino-2-hydroxy-(R)-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.042 mmol) was dissolved in dichloromethane (3 mL) and pyridine (0.3 mL). To the reaction mixture was then added at 0° C. (S)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride (13.8 mg, 0.055 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0° C. for one hour, then and the solvent evaporated in vacuo to yield a crude foam. The crude foam was dissolved in ethyl acetate

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131

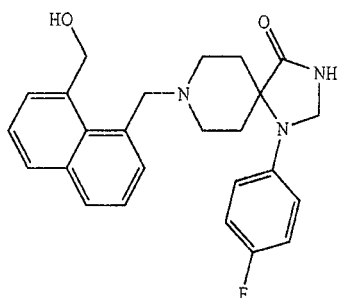
and successively washed twice with aqueous 0.5N HCl, twice with aqueous NaHCO₃, brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield the title compounds as a white foam.

¹H NMR (400 MHz, CDCl₃) δ 7.68–7.59 (3H, m), 7.55–7.39 (8H, m), 7.03–6.99 (2H, m), 6.98–6.93 (2H, m), 4.95–4.92 (1H, m), 4.70 (1H, d, J=4.8 Hz), 4.65 (1H, d, J=4.9 Hz), 3.99–3.97 (1H, s), 3.76 (1H, s), 3.57–3.29 (5H, m), 3.08–3.00 (2H, m), 2.79–2.76 (1H, m), 2.46–2.37 (1H, m), 2.37–2.29 (1H, m), 2.24–2.16 (1H, m), 2.00 (3H, s), 1.74–1.60 (4H, m)

MS (ES⁺) m/z 691.3 (M+H)⁺.

EXAMPLE 58

1-(4-Fluoro-phenyl)-8-(8-hydroxymethyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #734



Step A:

[8-(tert-Butyl-dimethyl-silanyloxymethyl)-naphthalen-1-yl]-methanol (*Aust. J. Chem.* 1996, 49, 793–800) (0.2 g, 0.66 mmol) was dissolved in dichloromethane (8 mL). To the solution was then added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3 (1H)-one, also known as Dess-Martin periodinane (0.56 g, 1.32 mmol). The reaction mixture was stirred for 1 hr then partitioned with an aqueous saturated solution of thiosulfate and dichloromethane. The organic layer was washed with an aqueous saturated solution of thiosulfate, an aqueous saturated solution of sodium bicarbonate, brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol/dichloromethane) to yield 8-(tert-butyl-dimethyl-silanyloxymethyl)-naphthalene-1-carbaldehyde as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 10.73 (1H, s), 8.05–7.98 (2H, m), 7.86–7.84 (1H, m), 7.65–7.63 (1H, m), 7.55–7.48 (2H, m), 5.07 (2H, s), 0.83 (9H, s), 0.01 (6H, s)

Step B:

1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.056 g, 0.22 mmol) and 8-(tert-butyl-dimethyl-silanyloxymethyl)-naphthalene-1-carbaldehyde (0.067 g, 0.22 mmol) were dissolved in dry 1,2-dichloroethane (5 mL). To the reaction mixture was added crashed 4A Molecular Sieve (0.028 g), a catalytic amount of glacial acetic acid. The reaction mixture was stirred at room temperature for 1 hr and it was then added at room temperature sodium triacetoxyborohydride (0.071 g, 0.33 mmol) under nitrogen atmo-

132

sphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with water and dichloromethane. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via semi-preparative HPLC (aqueous 0.5% TFA/acetonitrile) to yield crude 8-[8-(tert-butyl-dimethyl-silanyloxymethyl)-naphthalen-1-ylmethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one which was directly used to the next step.

Step C:

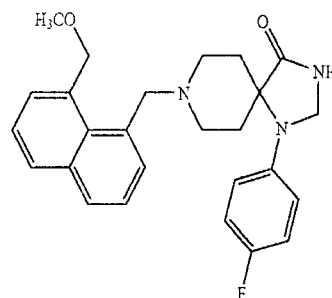
To the crude intermediate prepared as in STEP B was added acetonitrile (5 mL) and aqueous 5% TFA (5 mL). The reaction mixture was stirred at room temperature for 6 hrs. The solvent was then evaporated in vacuo to yield the title compound as a solid.

¹H NMR (400 MHz, CDCl₃) δ 8.85 (1H, br s), 7.86–7.81 (2H, m), 7.53–7.51 (1H, m), 7.43–7.33 (3H, m), 6.98–6.92 (2H, m), 6.84–6.79 (2H, m), 6.55 (1H, s), 5.12 (2H, br s), 4.66 (2H, s), 4.33 (1H, br s), 3.03–2.93 (4H, m), 2.38–2.31 (2H, m), 1.79–1.75 (2H, m)

MS (ES⁺) m/z 420.1 (M+H)⁺.

EXAMPLE 59

1-(4-Fluoro-phenyl)-8-(8-methoxymethyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one
Compound #733



Step A:

(8-Methoxymethyl-naphthalen-1-yl)-methanol (*Tetrahedron Lett.* 1997; 38, 8161–8164) (0.36 g, 1.8 mmol) was dissolved in dichloromethane (10 mL). To the solution was then added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3 (1H)-one, also known as Dess-Martin periodinane (1.5 g, 3.6 mmol). The reaction mixture was stirred for 1 hr, then partitioned with an aqueous saturated solution of thiosulfate and dichloromethane. The organic layer was washed with an aqueous saturated solution of thiosulfate, an aqueous saturated solution of sodium bicarbonate, brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield crude 8-methoxymethyl-naphthalene-1-carbaldehyde which was used directly into the next step.

Step B:

1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.45 g, 1.8 mmol) and crude 8-methoxymethyl-naphthalene-1-carbaldehyde (0.35 g, 1.8 mmol) were dissolved in dry dichloromethane (25 mL), dry 1,2-dichloroethane (5

133

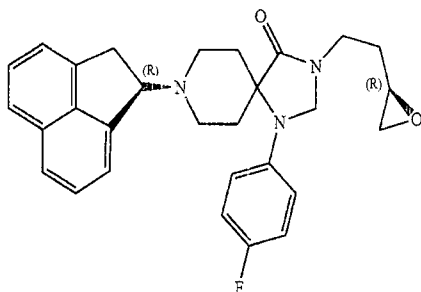
mL) and glacial acetic acid (0.5 mL). The reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was then added, at room temperature, sodium triacetoxyborohydride (0.57 g, 2.7 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 4 days. The reaction mixture was partitioned with water and dichloromethane. The organic layer was washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (40% ethyl acetate in hexanes) to yield the title compound as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.85–7.80 (2H, m), 7.60–7.58 (1H, m), 7.49–7.37 (3H, m), 6.94–6.83 (4H, m), 6.12 (1H, s), 5.23 (2H, s), 4.64 (2H, s), 4.10 (2H, s), 3.38 (3H, s), 2.91–2.81 (4H, m), 2.30–2.23 (2H, m), 1.73–1.70 (2H, m)

MS (ES⁺) m/z 434.2 (M+H)⁺.

EXAMPLE 60

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(2-(R)-oxiranyl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #723



(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.25 g, 0.62 mmol) was dissolved in N,N-dimethylformamide (2.0 mL). To the reaction mixture was then added at 0° C. sodium hydride (60% in mineral oil, 0.03 g, 0.80 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0° C. for 30 minutes. To the reaction mixture was then added, at 0° C., 2-(R)-(2-bromo-ethyl)-oxirane (0.14 g, 0.93 mmol). The reaction mixture was stirred at 0° C. under nitrogen atmosphere for 1 hr, then room temperature for 18 hours and then partitioned with water and ethyl acetate. The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (6% methanol/dichloromethane) to yield the title compound as a foam.

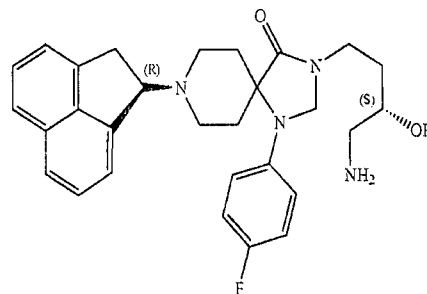
¹H NMR (400 MHz, CDCl₃) δ 7.70–7.65 (1H, m), 7.59 (1H, d, J=8.2 Hz), 7.54–7.50 (2H, m), 7.43 (1H, t), 7.26 (1H, d), 7.04–6.93 (4H, m), 4.95 (1H, dd, J=3.4 and 7.8 Hz), 4.64 (2H, dd, J=4.3 and 10.7 Hz), 3.64–3.50 (3H, m), 3.38–3.31 (1H, m), 3.19–3.03 (2H, m), 2.97–2.92 (1H, m), 2.83–2.80 (1H, m), 2.75–2.73 (1H, m), 2.48–2.39 (3H, m), 2.29–2.21 (1H, m), 2.03–1.95 (1H, m), 1.75–1.62 (3H, m)

MS (ES⁺) m/z 472.2 (M+H)⁺.

134

EXAMPLE 61

(R)-8-Acenaphthen-1-yl-3-(4-amino-3-(S)-hydroxy-butyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #722



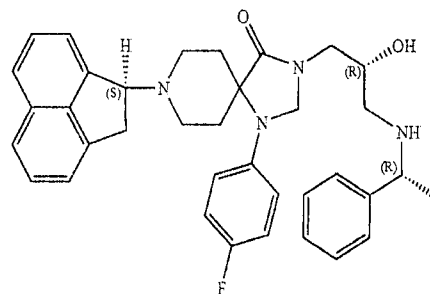
(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(2-(R)-oxiranyl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.03 g, 0.06 mmol) was dissolved in ethyl alcohol (1.0 mL). To the solution was then added concentrated ammonium hydroxide (1.0 mL) and the reaction mixture was stirred at 40° C. for 7 hrs in a pressure flask. The solvent was then evaporated in vacuo to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol/dichloromethane) to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.70–7.65 (1H, m), 7.59 (1H, d, J=8.2 Hz), 7.54–7.50 (2H, m), 7.43 (1H, t), 7.26 (1H, d), 7.04–6.93 (4H, m), 4.96–4.94 (1H, m), 4.64 (2H, dd, J=4.3 and 10.7 Hz), 3.86–3.76 (1H, m), 3.57–3.45 (2H, m), 3.39–2.98 (4H, m), 2.85–2.76 (2H, m), 2.65–2.58 (1H, m), 2.52–2.40 (2H, m), 2.32–2.24 (1H, m), 2.10–1.90 (3H, m), 1.76–1.51 (4H, m)

MS (ES⁺) m/z 489.1 (M+H)⁺.

EXAMPLE 62

8-(S)-Acetonaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-(R)-hydroxy-3-(1-phenyl-ethylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #663



8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(S)-oxiranyl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.45 g, 0.98 mmol) and R-(+)-α-methylbenzyl amine (0.178 g, 1.47 mmol) were dissolved in ethanol (3 mL). The reaction mixture was heated at 120° C. and microwaved for 600 sec. The solvent was evaporated in vacuo to yield an oil. The crude oil was purified via flash chromatography (80% ethyl acetate/heptane) to yield the title compound as a solid.

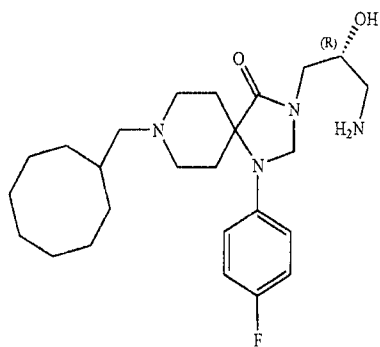
135

¹H NMR (300 MHz, CDCl₃) δ 7.65 (1H, t), 7.60 (1H, d, J=8.2 Hz), 7.50–7.54 (2H, d, J=5.1 Hz), 7.44 (1H, t), 7.07–7.28 (6H, m), 6.8–7.0 (4H, m), 4.9 (1H, m), 4.6 (2H, s), 3.8 (2H, m), 3.25–3.55 (5H, m), 2.95–3.1 (2H, m), 2.78–2.82 (1H, m), 2.6 (1H, m), 2.1–2.4 (5H, m), 1.5 (2H, m), 1.3 (3H, d)

MS (ES⁺) m/z 579.2 (MH⁺), 427.2

EXAMPLE 63

3-(3-Amino-2-(R)-hydroxy-propyl)-8-cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #620



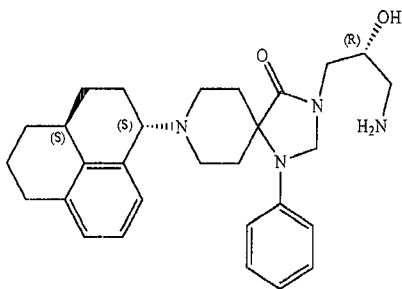
Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.71 g, 1.65 mmol) was dissolved in absolute ethanol (5 mL), then mixed with ammonium hydroxide (2 mL, 14.4 mmol) and heated to 120° C. and microwaved for 600 sec. The solvent was evaporated and the resulting residue was purified by column chromatography (80% ethyl acetate/heptane) to yield the title compound as an oil.

MS (electrospray)=447.4 (MH⁺)

¹H NMR (300 MHz, CDCl₃) δ 1.1–1.3 (m, 2H), 1.4–1.8 (m, 16H), 2.1 (d, 2H), 2.2–2.38 (m, 2H), 2.6–2.8 (m, 5H), 2.8–3.0 (m, 2H), 3.3–3.6 (m, 2H), 3.7–3.8 (m, 2H), 4.7 (s, 2H), 6.8–7.0 (m, 4H).

EXAMPLE 64

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1,3,8-triaza-spiro[4.5]decan-4-one dihydrochloride Compound #640



1-(4-Fluoro-phenyl)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]de-

136

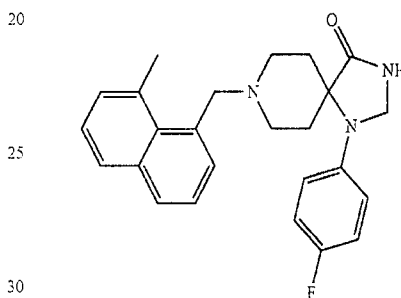
can-4-one (60 mg, 0.131 mmol) was dissolved in absolute ethanol (1 mL), then mixed with ammonium hydroxide (0.3 mL) and heated to 120° C. and microwaved for 480 sec. The solvent was evaporated. The resulting residue was dissolved in ethyl acetate and then treated with HCl in diethyl ether (1M, 1 mL) to yield the title compound as a solid.

MS (electrospray)=475.2 (MH⁺), 305.1

¹H NMR (300 MHz, CD₃OD) δ 0.9–1.0 (m, 1H), 1.1–1.5 (m, 5H), 1.7–1.8 (m, 1H), 2.0–2.25 (m, 6H), 2.3–2.7 (m, 4H), 2.7–3.2 (m, 7H), 3.32–3.7 (m, 2H), 3.85–4.2 (m, 2H), 4.9 (m, 2H), 6.9–7.4 (m, 8H)

EXAMPLE 65

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #547



Step A: (8-Hydroxymethyl-naphthalen-1-yl)-methanol

A 12-L 4-neck flask equipped with a thermocouple, an overhead stirrer, a 2-L addition funnel, and a condenser under N₂ was charged with 1,8-naphthalic anhydride (200 g, 1.0 mol) in toluene (2.5 L) at room temperature. The reaction mixture was agitated while adding DIBAL-H (1.5 M in toluene, 2.664 L, 4 mol) via the addition funnel over 1.5 h. The solution was then heated to 95° C. overnight, cooled to 15° C. and then slowly diluted with ethyl acetate (2.2 L) and H₂O (2 L) followed by addition of concentrated HCl (320 mL). The resulting suspension was stirred for 30 min at room temperature, filtered, and air dried on the filter for 2 h. The resultant material was in 95% ethanol (1.2 L), stirred at 70° C. for 2 h, and filtered to yield a wet solid which was air dried overnight on the filter and then dried at 70° C. in a vacuum oven to yield (8-hydroxymethyl-naphthalen-1-yl)-methanol as a solid;

¹H NMR (400 MHz, CD₃OD) δ 7.85 (2H, dd, J=1.3 and 8.2 Hz), 7.61 (2H, dd, J=1.0 and 7.0 Hz), 7.46–7.42 (2H, m), 5.22 (2H, s), 4.82 (4H, s).

Step B: 1H,3H-Benzo[de]isochromene

A 1-L 3-neck flask equipped with an overhead stirrer, a condenser, and a thermocouple was charged with (8-hydroxymethyl-naphthalen-1-yl)-methanol (33.0 g, 0.175 mol), concentrated phosphoric acid (225 mL), and water (5 mL). The reaction mixture was stirred at 140° C. for 3 h, cooled to room temperature, diluted with CH₂Cl₂ (800 mL) and transferred to a 2-L separatory funnel. After washing the organic layer with water and saturated NaHCO₃ it was dried over MgSO₄ and evaporated to yield 1H,3H-Benzo[de]isochromene as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ 6.96–6.92 (2H, m), 6.62–6.58 (2H, m), 6.39–6.37 (2H, m), 4.17 (3H, s).

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-055461- -00006-0000

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 055461
Asunto : Oposición a la solicitud de patente de Invención titulada
"METODOS PARA EL TRATAMIENTO DEL ABUSO,
ADICCION Y DEPENDENCIA DEL ALCOHOL"
Solicitante : JANSSEN PHARMACEUTICA N.V.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 619 del 19 de agosto de 2010

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** Conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "METODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCION Y DEPENDENCIA DEL ALCOHOL", cuyos titulares son **JANSSEN PHARMACEUTICA N.V.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

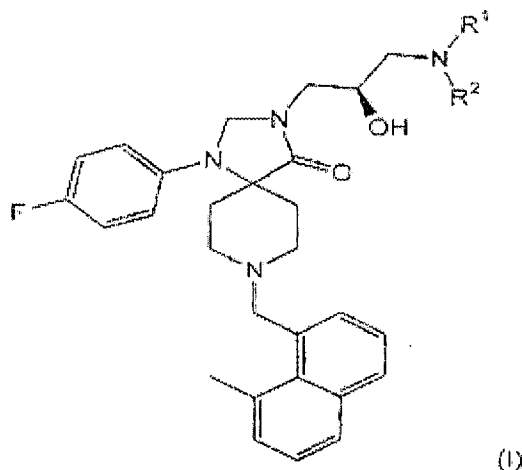
1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular MODULADORES DE ORL-1. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

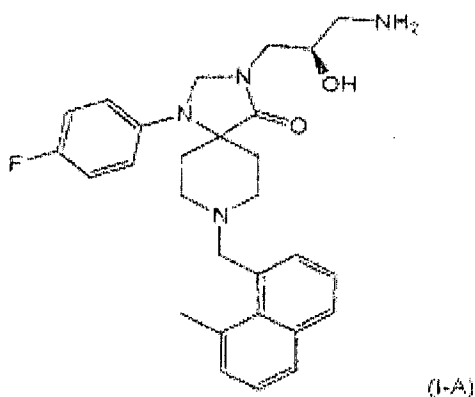
2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 29 de mayo de 2009 reivindicando prioridad bajo la solicitud US20060861375 del 2006-11-28; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 619 del 19 de agosto de 2010, cuya publicación internacional corresponde a la WO2008067177 del 2008-06-05.

2.2. La solicitud colombiana 09 055461 objeto de la presente oposición se refiere a un método de tratamiento del abuso, adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I):



en donde: R1 y R2, cada uno independientemente, se seleccionan del grupo que consiste en hidrógeno y alquilo de C1-4; o una sal farmacéuticamente aceptable del mismo; solo o en una terapia combinada con al menos un agente contra la adicción. El método de tratamiento del abuso, adicción o dependencia del alcohol, según la solicitud comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A):



o una sal farmacéuticamente aceptable del mismo, método en donde el compuesto de fórmula (I-A) o su sal farmacéuticamente aceptable es una sal monosulfato cristalina de un compuesto de fórmula (I-A) y donde el abuso, adicción o

dependencia del alcohol es el abuso del alcohol o la dependencia del alcohol, y el ansia de alcohol.

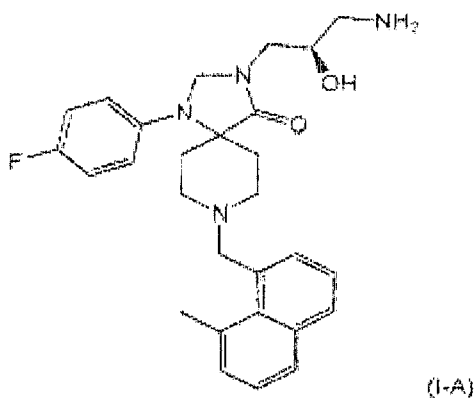
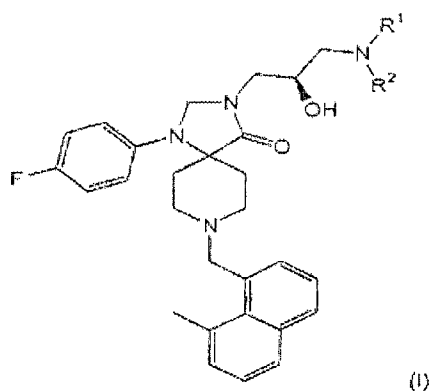
2.3. En primera instancia, se debe advertir que en el capítulo reivindicatorio de la solicitud objeto de la presente oposición, se hace referencia a los usos de la composición en la medicina, no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso no sería patentable.

2.4. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*, tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: US7081463 publicada el 25 de mayo de 2006.

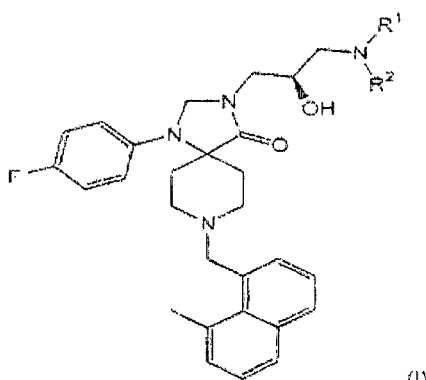
2.5. Ahora bien, el documento D1, se refiere a derivados de 1, 3, 8-triazaspiro [4.5] decan-4-ona hidroxil alquilo sustituidos, útiles en el tratamiento de los trastornos y condiciones mediadas por el receptor de ORL-1 acoplado a la proteína G. Más

concretamente, los compuestos revelados en dicho documento D1 son útiles en el tratamiento de los trastornos y las enfermedades como ansiedad, depresión, pánico, demencia, manía, trastorno bipolar, abuso de sustancias, dolor neuropático, el dolor agudo, dolor de la migraña crónica, asma, tos, psicosis, esquizofrenia, epilepsia, hipertensión, obesidad, trastornos alimentarios, ansiedad, diabetes, arritmia cardíaca, síndrome del intestino irritable, enfermedad de Crohn, incontinencia urinaria, trastornos suprarrenales, el trastorno por déficit de atención (ADD), déficit de atención con hiperactividad (TDAH), enfermedad de Alzheimer, para mejorar la cognición o la memoria y para la estabilización del estado de ánimo. El Documento D1, particularmente en los ejemplos 34 y 50 describe el uso de compuestos pertenecientes a las fórmulas I, e IA:



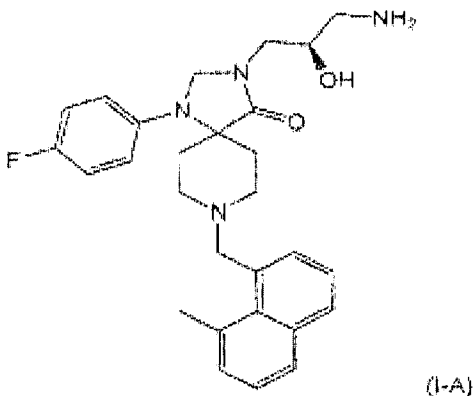
y una lista de sales, tales como la sal de sulfato. Adicionalmente según dicho documento D1, el tratamiento al que está dirigido, se puede aplicar a una lista de trastornos, entre los que se encuentran el abuso de sustancias y el deseo (ansia). Los compuestos 3- (3-Amino-2-(R)-hydroxy-propyl)- 1- (4-fluoro-phenyl)- 8 -(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one y 3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1- (4-fluoro-phenyl)-8- (8-methyl-naphthalen-1-ylmethyl)-1, 3, 8-triaza-spiro [4.5]decan-4-one, correspondientes a los ejemplos 34 y 50 se describen adicionalmente como ligados del receptor ORL-1 acoplado a la proteína G (ORL-1 G protein receptor ligands). La solicitud objeto de la presente oposición no es novedosa pues lo reclamado ya era parte de arte anterior.

2.6. Tomando el documento D1 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1 por sí solo, concebir un método de tratamiento del abuso, adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I):



(I)

y/o una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A):



o una sal farmacéuticamente aceptable del mismo, teniendo en cuenta que dichos compuestos son conocidos para el tratamiento de abuso y ansia de sustancias en general. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 055461 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con ninguno de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARENCIA DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”* A la fecha de prioridad, 28 de noviembre de 2006 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, un método de tratamiento del abuso,

adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), en donde: R1 y R2, cada uno independientemente, se seleccionan del grupo que consiste en hidrógeno y alquilo de C1-4; o una sal farmacéuticamente aceptable del mismo; solo o en una terapia combinada con al menos un agente contra la adicción. El método de tratamiento del abuso, adicción o dependencia del alcohol, según la solicitud comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A), o una sal farmacéuticamente aceptable del mismo, método en donde el compuesto de fórmula (I-A) o su sal farmacéuticamente aceptable es una sal monosulfato cristalina de un compuesto de fórmula (I-A) y donde el abuso, adicción o dependencia del alcohol es el abuso del alcohol o la dependencia del alcohol, y el ansia de alcohol; sobre lo cual busca protección en el capítulo reivindicatorio.

- 2.8.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 28 de noviembre de 2006, a partir del documento D1 por sí solo, un experto en la materia puede llegar de manera evidente a tomar compuestos conocidos para el tratamiento de abuso y ansia de sustancias en general y concebir un método de tratamiento del abuso, adicción o dependencia del alcohol, que comprende administrar a un sujeto en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), o administrar a un sujeto en necesidad

del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I-A); sobre lo cual busca protección en el capítulo reivindicatorio.

2.8.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, en el capítulo reivindicatorio se reclaman usos y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumple con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con ninguno de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **“METODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCION Y DEPENDENCIA DEL ALCOHOL”**, cuyos titulares son **JANSSEN PHARMACEUTICA N.V.**, solicitud Colombiana que apareció

publicada en la Gaceta de la Propiedad Industrial N° 619 del 19 de agosto de 2010.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US7081463 publicada el 25 de mayo de 2006.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.

4. Copias de los documentos:

- D1: US7081463 publicada el 25 de mayo de 2006.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
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