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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-008212- -00007-0000

Fecha: 2008-04-15 10:21:43 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 74

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [X] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: **07-08212**
Solicitante: **ZAMBON GROUP S. P. A**
Apoderado: **DILIA MARIA RODRIGUEZ**
Título de la nueva creación o denominación del signo: **"UNA COMPOSICION FARMACEUTICA QUE COMPRENDE GABAPENTINA.".**
Gaceta: **587**

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: **PROCAPS S.A**
Dirección: **CALLE 80 No. 78B -201**
Nacionalidad o Domicilio: **COLOMBIA**
Lugar de Constitución: **BARRANQUILLA**
Teléfono: **(571)3719900** Fax: **(571)3730818**
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [X]
C.E. [ ] Otro [ ]
Cual ____
Número **890.106.527-5**

REPRESENTANTE O APODERADO

Nombre: **ELIANA ISAURA MORENO BOHORQUEZ**
Dirección: **CARRERA 13 No. 119-95 OF 104**
Teléfono: **(571)2131213** Fax: **(571)6121979**
E-mail: **negocios@optimum-co.com**

IDENTIFICACIÓN
C.C. [ ] NIT [X]
C.E. [ ] Otro [ ]
Cual ____
Número **51.975.664** TP **83823**

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: **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".

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⑤ **Comprobante de pago No.** _____ **Fecha** _____

⑥ **ANEXOS**

- [x] Comprobante de pago de la tasa.
- [x] Poderes, si fuere el caso.
- [x] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso.
- [x] 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

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 07008212
Asunto	: Oposición a la solicitud de patente de Invención titulada "UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE GABAPENTINA"
Solicitante	: ZAMBON GROUP S. P. A
Opositora	: PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 587 del 18 de enero de 2008

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

Carrera 13 N° 119-95, Oficina 104. Tel. (571) 2 13 12 13 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

del registro de la Patente de Invención titulada **"UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE GABAPENTINA"**, cuyo titular es **ZAMBON GROUP S. P. A.**, 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 legitimo 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 gabapentina. 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 enero de 2007, reivindicando prioridad bajo la solicitud IT2004MI01447 del 2004-07-20; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008, cuya publicación internacional corresponde a la WO2006008295 del 2006-01-26.

2.2. La solicitud colombiana **07008212** objeto de la presente oposición, se refiere a una composición farmacéutica estable que comprende gabapentina como ingrediente activo, caracterizado en que esta también comprende una mezcla de excipientes capaces de no promover la conversión de gabapentina en la impureza lactámica correspondiente, que comprende: (i) un agente de deslizamiento seleccionado a partir de sal de calcio de un ácido débil, (ii) un agente de lubricación seleccionado de aceite de castor hidrogenado y de behenato de glicerilo; y opcionalmente (iii) un agente de dilución, solo o mezclado con uno o más de otros agentes de dilución, seleccionados a partir de azúcar monosacaridico tal como sorbitol, xilitol, manitol, fructosa, dextrosa y eritritol y derivados de polisacaridos como sacarosa, manitol, isomalt, maltitol, un galactomanan, ácido alginico o una de sus sales, una pectina, un carragenanos y maltodextrina.

2.3. En primera instancia, se debe advertir que las reivindicación 14 se refiere al uso y 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 seria patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra 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*". Así las cosas, 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 afecta la patentabilidad de la presente solicitud:

- D1: WO2004014356 publicada el 19 de febrero de 2004.
- D2: US2004010035 publicada el 15 de enero de 2004.
- D3: US2004092522 publicada el 13 de mayo de 2004

2.5. Ahora bien, el documento D1 se relaciona con composiciones farmacéuticas que comprenden gabapentina de estabilidad mejorada en adición con un compuesto básico tal como un hidróxido. Particularmente en las páginas 2, línea 7 a 19, página 3 línea 1 8 a 16 y ejemplos de preparación revela la estabilización de la gavapentina a través de una formulación con una sal hidróxido metálica de un ácido lábil, preferiblemente de una sal sódica, donde el uso de lubricantes es indicado. Por su parte, el documento D2 se relaciona con composiciones y métodos para tratar y/o prevenir desórdenes gastrointestinales en pacientes mamíferos. Dicha anterioridad D2 define en el párrafo 0082 y ejemplo 1, la combinación de gavapentina con tricalcio fosfato en forma de polvo de relleno de cápsulas. Ahora bien, el documento D3 se relaciona con una combinación de un ligante alfa-2-delta y un inhibidor PDEV para el empleo en el tratamiento curativo, profiláctico o paliativo de dolor, en particular dolor neuropático. Según esta anterioridad D3, las sustancias preferidas son gabapentina y pregabalina. Particularmente en el párrafo 0204 de dicho documento D3 se revelan formulaciones de gavapentina sólidas, que incluyen calcio carbonato y calcio fosfato dibasico que son indicados como excipientes y como lubricantes gliceril behenato. Por lo tanto, en vista de las indicaciones reveladas en D1 cualquier persona versada en la materia puede llegar de manera evidente y obvia a combinar tricalcio

fosfato tal y como se indica en D2 con el agente lubricante revelado en D3, para llegar a la materia aquí propuesta. Por lo tanto, vistos dichos documentos D2 y D3 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

2.6. Por lo tanto, este documento objeto de oposición con base en dichos documentos D2 y D3 en combinación con el documento D1, carece de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **07008212** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. <u>CARENCIA DE ALTURA INVENTIVA</u>. 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, 20 de julio de 2004, a partir de las indicaciones reveladas en D1 cualquier persona versada en la materia puede llegar de manera evidente y obvia a combinar tricalcio fosfato tal y como se indica en D2 con el agente lubricante

revelado en D3, para llegar a la materia sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. <u>CARENCIA DE APLICACIÓN INDUSTRIAL</u> 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, algunas cláusulas reclaman el método terapéutico 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 cumplen 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 dos 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 negar el registro Patente de invención denominada **"UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE GABAPENTINA"**, cuyo titular es **ZAMBON GROUP S. P. A.,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° **587 del 18 de enero de 2008.**

3. PRUEBAS

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

- D1: WO2004014356 publicada el 19 de febrero de 2004.
- D2: US2004010035 publicada el 15 de enero de 2004.
- D3: US2004092522 publicada el 13 de mayo de 2004

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: WO2004014356 publicada el 19 de febrero de 2004.
- D2: US2004010035 publicada el 15 de enero de 2004.
- D3: US2004092522 publicada el 13 de mayo de 2004

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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 Nº 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.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-008212- -00007-0000

Fecha: 2008-04-15 10:21:43 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYI Eve: 378 FASENACIONALI
Act: 400 OPOSIOBSERVTER Folios: 74

RECIBO OFICIAL DE CAJA : 08 - 30,322
FECHA : ABRIL 15 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	4767293	09/04/2008	1,596,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL : $	266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

106

PROCAPS

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. **07.008.212,** titulada "**UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE GABAPENTINA",** cuyo titular es **ZAMBON GROUP S. P. A.,** publicada en la gaceta No. 587 del 18 de Enero de 2008.

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 administrativa y judicialmente 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 7 días del mes de Abril de 2008.

PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

CERTIFICA

Que la(s) firma(s) que aparece(n) en el documento que antecede se asemeja(n) a la(s) de WALTER TANAKA TATEKAWA

Que aparece(n) registrada(s) en esta Notaría previa confrontación de la(s) misma(s).

(Decreto 2601/70)

Barranquilla 08 de ABRIL de 2008

LA NOTARIA

REPUBLICA DE COLOMBIA NOTARIA SEGUNDA 2a. MARTA L. ROJAS ZAMBRANO Notaria Encargada CIRCULO DE BARRANQUILLA

PRESENTACIÓN PERSONAL

El anterior escrito fue presentado ante la NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTÁ, D.C.

personalmente por [illegible]

quien exhibió la c.c. 51975664 de [illegible]

y Tarjeta Profesional No. 83823 C.S.J.

Fecha 14 ABR. 2008

Gonzalo Espinel Quintana

NOTARIO (E)

REPUBLICA DE COLOMBIA NOTARIA 18 DE BOGOTÁ, D.C.

107 AS

03-13008341 024802 PROCAPS S.A.
Barranquilla, 08 de Abril de 2008 Hr:11:57:10

No. 12309273

CAMARA DE COMERCIO DE BARRANQUILLA

********** 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
10**********

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

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

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

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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

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 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 Cámara 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

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.

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

03-13008341 024802 PROCAPS S.A.
Barranquilla, 08 de Abril de 2008 Hr:11:57:10

No. 12309274

CAMARA DE COMERCIO DE BARRANQUILLA

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

DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24,802.

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 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 y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-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, d) 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. e)La compra,venta,exportacion y disdistribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionacionales 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; g) Prestar los servicios de asesoria 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, cosmeticos y farmaceuticos para uso humano, animal o in-

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dustrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, 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 gravamenes sobre bienes muebles e inmuebles; designar representantes o 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 obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravamenes reales sobre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2,000,000,000	**********2,000,000	**********1,000
Suscrito		
$**********1,224,500,000	**********1,224,500	**********1,000
Pagado		
$**********1,229,071,000	**********1,229,071	**********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 requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir

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

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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 siguentes 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 gravamenes 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 identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta

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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 gravamenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. ----------

C E R T I F I C A

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	CC.*******7,463,982
2. Minski Gontovnik Meyer	CC.*******7,461,324
3. Minski Gontovnik Jose	CC.*******8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.******72,219,541
2. Minski Deitel Daniel	.****************
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

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

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

CAMARA DE COMERCIO DE BARRANQUILLA

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PROCAPS S.A.----------
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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
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.******32,696,645

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

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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

Que 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:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.******32,748,111

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 condicion de Presidente y ------- Representante Legaql de la sociedad PROCAPS S.A., el 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 ningun 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 que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS

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

03-13008341 024802 PROCAPS S.A.
Barranquilla, 08 de Abril de 2008 Hr:11:57:10

No. 12309277

CAMARA DE COMERCIO DE BARRANQUILLA

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

MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ------- liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. 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 senor WILLIAM ALBERTO BARROS CERRA ---------- CC.No.8.715.941, y al senor ANTONIO VARELA DIAZ CC.No.72.004.699, para que en nombre y representacion 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 tambien los demas documentos relacionados con ellas, ---------- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al senor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al senor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de ------ PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites 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 ---------- representacion de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ---------- (1.000.000.000.00) M.L. CUARTO: EI 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 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: 19 de Marzo de 2008.

La información sobre embargos de establecimiento se suministra en

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

ANEXO 1

Carrera 13 Nº 119-95, Oficina 104. Tel. (571) 2 13 12 13 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

D1 118

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(30) Priority Data:
2,395,931 7 August 2002 (07.08.2002) CA

(71) Applicant and
(72) Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50 Old Colony Road, Toronto, Ontario M2L 2K1 (CA).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/014356 A1

(54) Title: SOLID COMPOSITIONS COMPRISING GABAPENTIN HAVING IMPROVED STABILITY

(57) Abstract: Solid pharmaceutical compositions of improved stability which comprise gabapentin and a basic compound that is a hydroxide or a salt of a weak acid.

SOLID COMPOSITIONS COMPRISING GABAPENTIN HAVING IMPROVED STABILITY

Background of the Invention

Gabapentin is a compound that is disclosed in U.S. patents 4,024,175 and 4,087,544, and is useful in therapy of certain cerebral disorders such as epilepsy.

Gabapentin is known to be susceptible to degradation into an impurity known as gabapentin lactam.

U.S. patent 6,054,482 discloses that in order to produce a stable composition comprising gabapentin it is necessary to do as follows:

1. Produce the gabapentin such that it contains less than 20 ppm of an ion of a mineral acid; and

2. Carefully select the excipients (inactive ingredients) used in the composition to exclude any excipient that catalyzes the degradation.

In the manufacture of hard gelatin capsules containing gabapentin, it is relatively simple to avoid use of excipients that catalyze degradation, because it is possible to fill capsules with gabapentin with no excipients at all, or with a minimal amount of excipients.

However, in the case of tablets comprising gabapentin, it is necessary to add a binder to give tablets of suitable hardness, as well as a lubricant to avoid sticking and binding in the tabletting process; and it is difficult if not impossible to find suitable excipients which enable satisfactory stability, especially if the gabapentin being used contains over 20 ppm of an ion of a mineral acid.

It is thus desirable to find a means of improving the stability of solid compositions that comprise gabapentin along with at least one excipient.

Description of the Invention

It has been found that the stability of a solid composition comprising gabapentin can be significantly improved by inclusion of a relatively small amount of basic compound that is a hydroxide or a salt of a weak acid.

Compositions of the present invention thus are solid compositions comprising gabapentin, at least one excipient other than a basic compound that is a hydroxide or a salt of weak acid, and at least one excipient that is a basic compound that is a hydroxide or a salt of a weak acid, such as, for example, a carbonate, bicarbonate, or phosphate.

The basic compound will preferably be sodium hydroxide or a sodium salt of a weak acid, such as, for example, sodium carbonate, sodium bicarbonate, and tribasic sodium phosphate.

The amount of the basic compound relative to the amount of gabapentin by weight will preferably be under 5%, will more preferably be from about 0.01% to about 4%, and will even more preferably be from about 0.02% to about 1%.

The composition may be made by either a dry mix process (in which the ingredients are mixed without the use of a solvent) or by a wet granulation process in which a solvent is used and then evaporated.

The wet granulation process is preferable as it enables tablets of greater hardness.

The process will preferably include the steps of dissolving a binder (such as copolyvidone, povidone, or hydroxypropyl cellulose) in solvent, granulating the gabapentin with the solution, and drying to evaporate the solvent. The solvent may be water, but will preferably be or comprise an organic solvent, such as methanol, ethanol or methylene chloride.

The basic compound may be mixed with the gabapentin in dry form before the wet granulation is done. However, the basic compound will preferably be added to and mixed into the solution of the polymer in solvent before the solution is used to wet granulate the gabapentin.

After the granulation is complete and the solvent has been evaporated, the dried material will preferably be mixed with a lubricant, such as magnesium stearate, and optionally other excipients such as, for example, croscarmellose sodium as disintegrant.

The final mixture will then be compressed into tablets, which will optionally then be film-coated.

The invention will be better understood from the following examples, which are meant to be illustrative, and not limiting of the scope of the invention.

Example 1

Solutions A and B were prepared with ingredients in the following proportions:

Solution A:	Copolyvidone	24.9 parts
	Methylene Chloride	50.0 parts
		74.9 parts

Solution B:	Sodium Carbonate anhydrous	0.1 part
	Water	1.0 part
		1.1 part

Solution B was then added to and blended into Solution A and the resultant mixture was used to granulate 100 parts of gabapentin. After drying to evaporate the methylene chloride and water, the content of the dried mass was as follows:

Gabapentin	100.0 parts
Copolyvidone	24.9 parts
Sodium carbonate	0.1 part
	125.0 parts

The stability of the resulting material was compared to that of material similarly prepared but without any sodium carbonate. This was done by measuring the increase in content of gabapentin lactam after storage at 60°C for 48 hours.

The results as a percentage of the gabapentin were as follows:

Sample	Increase in Lactam
Material of example 1	0.07%
Similar material without sodium carbonate	0.16%

It can thus be seen that the inclusion of the sodium carbonate significantly reduced the rate of increase of the lactam.

Example 2

Ingredients were mixed in the following proportions:

Granules of example 1	1000
Magnesium stearate	3
Croscarmellose sodium	1
	1004

This mixture was compressed into tablets of weight 1004 mg each. Each tablet thus comprised 1000 mg of the granules of example 1, which in turn comprised 800 mg of gabapentin.

Claims

1. A solid pharmaceutical composition comprising gabapentin, a basic compound that is a hydroxide or a salt of a weak acid, and at least one other excipient that is not a hydroxide or a salt of a weak acid.

2. A composition of claim 1 wherein the basic compound is sodium hydroxide.

3. A composition of claim 1 wherein the basic compound is a sodium salt of a weak acid.

4. A composition of claim 1 wherein the basic compound is sodium carbonate.

5. A composition of claim 1 wherein the basic compound is sodium bicarbonate.

6. A composition of claim 1 wherein the basic compound is tribasic sodium phosphate.

7. A composition of any of claims 1 to 6 wherein the amount of the basic compound relative to the amount of gabapentin by weight is under 5%.

8. A composition of any of claims 1 to 6 wherein the amount of the basic compound relative to the amount of gabapentin is from about 0.01% to about 4%.

9. A composition of any of claims 1 to 6 wherein the amount of the basic compound relative to the amount of gabapentin is from about 0.02% to about 1%.

10. A composition of any of claims 1 to 9 wherein made by a process in which a binder is dissolved in a solvent, the solution is used to wet granulate the gabapentin, and the solvent is evaporated.

11. A composition of claim 10 wherein the basic compound is added to the solution of the binder in the solvent.

12. A composition of any of claims 1 to 11, which comprises a binder, selected from copolyvidone, povidone and hydroxypropyl cellulose.

13. A composition of any of claims 1 to 11, which comprises copolyvidone as binder.

14. A composition of any of claims 1 to 13 in the form of a tablet.

126 27

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01174

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 26263 A (SIGMAPHARM INC ;SPIREAS SPIRIDON (US)) 4 April 2002 (2002-04-04) paragraph '0009! paragraph '0023! ---	1-14
A	WO 02 45693 A (BYK GULDEN LOMBERG CHEM FAB ;LINDER RUDOLF (DE); NEY HARTMUT (DE);) 13 June 2002 (2002-06-13) page 12, last paragraph page 41, paragraph 3 ---	1-14
A	US 6 383 471 B1 (CHEN FENG-JING ET AL) 7 May 2002 (2002-05-07) claims 1,4,8 -----	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A" document defining the general state of the art which is not considered to be of particular relevance
'E" earlier document but published on or after the international filing date
'L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O" document referring to an oral disclosure, use, exhibition or other means
'P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2003	31/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Sindel, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 03/01174

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0226263 A	04-04-2002	US 2002091159 A1	11-07-2002
		AU 9473601 A	08-04-2002
		CA 2422871 A1	04-04-2002
		EP 1322335 A2	02-07-2003
		WO 0226263 A2	04-04-2002
WO 0245693 A	13-06-2002	AU 1607302 A	18-06-2002
		CA 2430828 A1	13-06-2002
		EE 200300235 A	15-08-2003
		WO 0245693 A1	13-06-2002
		EP 1341527 A1	10-09-2003
		NO 20032593 A	05-08-2003
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		CA 2366702 A1	12-10-2000
		EP 1165048 A1	02-01-2002
		WO 0059475 A1	12-10-2000

ANEXO 2

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D2 129

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Ciociola et al. (43) **Pub. Date: Jan. 15, 2004**

(54) **GASTROINTESTINAL COMPOSITIONS**

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Publication Classification

(51) **Int. Cl.**[7] **A61K 31/21**

(52) **U.S. Cl.** **514/506**

(57) **ABSTRACT**

The invention relates to compositions and methods for treating and/or preventing lower gastrointestinal (GI) disorders in mammalian patients, more particularly for alleviating and/or preventing the lower GI symptoms associated with such disorders.

GASTROINTESTINAL COMPOSITIONS

[0001] This Continuation-In-Part application claims priority to the utility application filed on Jul. 10, 2002 by Express Mail No. EL819323526US.

FIELD OF THE INVENTION

[0002] The invention relates to compositions and methods for treating and/or preventing lower gastrointestinal (GI) disorders in mammalian patients, more particularly for alleviating and/or preventing the lower GI symptoms associated with such disorders.

BACKGROUND OF THE INVENTION

[0003] The primary function of the gastrointestinal tract is the absorption of ingested nutrients. This is achieved when transit along the esophagus and gastrointestinal tract is at a rate which facilitates optimal digestion and absorption of water and electrolytes abnormal patterns in gastrointestinal motility result in number of disorders ranging from diffuse esophageal spasm (an esophageal obstructive disorder characterized by dysphagia), achalasia (an obstructive disorder in which the lower esophageal sphincter fails to relax adequately resulting in dysphagia) and noncardiac chest pain to functional bowel disorders such as the irritable bowel syndrome (IBS), non-ulcer dyspepsia, and idiopathic constipation.

[0004] IBS is particularly disturbing since it involves chronic episodes of diarrhea and/or constipation for which there is no identifiable organic cause. The disorder appears to result from faulty regulation in both the gastrointestinal and nervous systems.

[0005] Where drug therapy is indicated, the therapy includes prokinetic agents for constipation; anticholinergics, antispasmodics such as trimebutine, tricylic and serotonin reuptake inhibitor antidepressants, and sedatives for cramping pain; and opiates (such as loperamide and diphenoxylate) and cholestyramine for diarrhea. However, such therapy has proven to have limited, if any, efficacy.

[0006] Clearly, therefore, a significant unmet need remains for an efficacious and comprehensive treatment of patients afflicted with such lower GI disorders, including alleviation of such lower GI symptoms as chronic diarrhea, constipation and cramps.

[0007] The present inventors have found that gastrointestinal compositions comprising a gamma-aminobutyric acid analogs in combination with amino-ether and/or ester oxides provide a more comprehensive reduction in IBS symptoms as compared to previous drug therapies.

[0008] Accordingly, an aspect of the present invention is to provide gastrointestinal compositions.

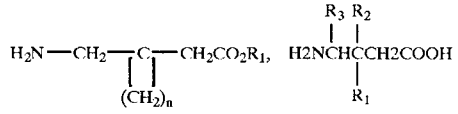
[0009] Another aspect of the present invention is to provide gastrointestinal compositions which prevent, reduce or alleviate the symptoms associated with IBS.

[0010] A further aspect of the present invention is to provide gastrointestinal compositions comprising gamma-aminobutyric acid analogs in combination with amino-ether and/or ester oxides.

SUMMARY OF THE INVENTION

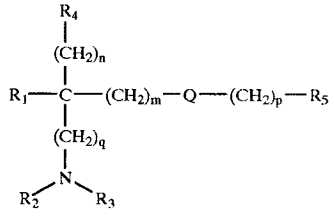
[0011] The present invention relates to compositions for treating or preventing gastrointestinal disorders, comprising:

[0012] a) a GABA analog of the formula selected from the group consisting of:



[0013] and mixtures thereof; and

[0014] b) an amino-ether and/or -ester oxide having the formula:



[0015] in which: R_1 is a lower alkyl, R_2 and R_3 which are the same or different are hydrogen or lower alkyl, R_4 is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents which are identical or different, halogen or lower alkoxy, R_5 is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical, Q is —O— or —COO—, n is equal to zero, 1 or 2, m and q are, independently of one another, equal to zero or to 1, p is an integer ranging from 0 to 9.

[0016] Methods of treating or preventing gastrointestinal disorders using the above compositions are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION

[0017] All percentages and ratios used herein are by weight of the total composition and all measurements made are at 25. degree. C., unless otherwise designated.

[0018] The compositions of the present invention can comprise, consist essentially of, or consist of, the essential as well as optional ingredients and components described herein. As used herein, "consisting essentially of" means that the composition or component may include additional ingredients, but only if the additional ingredients do not materially alter the basic and novel characteristics of the claimed compositions or methods.

[0019] All publications cited herein are hereby incorporated by reference in their entirety.

[0020] As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

[0021] By "safe and effective amount" is meant an amount of a compound or composition which is high enough to

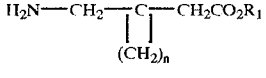
positively modify the condition being treated, but low enough to avoid serious side effects at a reasonable benefit/risk ratio within the scope of sound medical judgement. The safe and effective amount may vary with the age and physical condition of the person being treated, the severity of the condition, the specific ingredients employed, and like factors.

[0022] The phrase "gastrointestinal disorder", as used herein, means a disorder of the gastrointestinal tract, including the small and large intestines and the rectum, and/or symptoms usually attributed to a dysfunction of one or more of these organs, such as diarrhea, constipation and/or abdominal and lower abdominal cramping or pain. It is understood that gastro intestinal disorders include both disorders for which an organic cause (e.g. infection by a parasite) is known and disorders for which no organic cause can be ascertained, such as IBS. Gastrointestinal disorders, therefore, include, but are not limited to, irritable bowel syndrome, functional diarrhea, ulcerative colitis, collagenous colitis, microscopic colitis, lymphocytic colitis, inflammatory bowel disease, Crohn's disease, and infectious diarrhea such as diarrhea associated with amebiasis, giardiasis, a viral infection, cytomegalovirus infection, or a pathogenic bacterial infection. The bacterial infection may, for example, be an infection by a bacterium selected from the group consisting of a bacterium of the genus Escherichia, an *Escherichia coli* 0157:H7 bacterium, a bacterium of the genus Salmonella, a bacterium of the genus Shigella, a bacterium of the genus Campylobacter, a bacterium of the species *Campylobacter jejuni,* and a bacterium of the genus Yersinia

[0023] The gastrointestinal compositions of the present invention, including the essential and optional components thereof, are described in detail hereinafter.

[0024] Gamma-Aminobutyric Acid Analogs

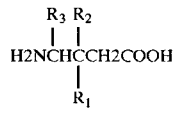
[0025] The compositions and methods of this invention utilize a safe and effective amount of a gamma-aminobutyric acid (GABA) analogs. A GABA analog is any compound derived from or based upon gamma-aminobutyric acid. The compounds are readily available, either commercially, or by synthetic methodology well known to those skilled in the art of organic chemistry. GABA analogs used in the present invention are cyclic amino acids of Formula I.



I

[0026] wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially useful embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 5, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin. Also useful herein are GABA analogs of Formula I wherein the cyclic ring is substituted, for example with alkyl groups such as methyl or ethyl.

[0027] Typical compounds include (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid. Compounds and embodiments of Formula I are described in more detail in U.S. Pat. No. 4,024,175; herein incorporated by reference in its entirety. Also useful in the present invention are GABA analogs of Formula II.



II

[0028] or a pharmaceutically acceptable salt thereof, wherein R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carboxyl. Diastereomers and enantiomers of compounds of Formula II can be utilized in the invention. An especially useful embodiment employs a compound of Formula II where R_2 and R_3 are both hydrogen, and R_1 is $-(CH_2)_{0-2}-iC_4H_9$ as an (R), (S), or (R,S) isomer.

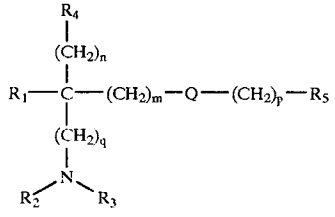
[0029] 3-(1-aminoethyl)-5-methylhexanoic acid, 3-aminomethyl-5-methyl-hexanoic acid, and (S)-3-(aminomethyl)-5-methylhexanoic acid (now known generically as pregabalin, as well as CI-1008) are also useful herein. Compounds and embodiments represented by Formula II can be found in U.S. Pat. No. 5,563,175, which is also incorporated herein by reference in its entirety.

[0030] The percentage of the active ingredient in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present, for example, from 10% to 90% by weight.

[0031] The amount of GABA analog in the composition will generally be from about 1 to about 300 mg per kg, preferably from about 5 to about 200 mg per kg, more preferably from about 10 to about 100 mg per kg of subject body weight. Typical doses will be from about 10 to about 5000 mg, preferably from about 20 to about 800 mg, per day for an adult subject of normal weight. It is expected that common doses that might be administered could be from 100 mg three times a day up to 600 mg four times a day. Useful intravenous dose is between about 5 and about 50 mg. (The intravenous dosage is within the dosing range used in treatment of gastrointestinal diseases such as ulcers and IBS, or as would be dictated by the needs of the patient as described by the physician.) A more complete description of acceptable GABA analog effective amounts thereof for use in unit dose compositions of the present invention can be found in U.S. Pat. Nos. 6,127,418 and 6,117,908, both of which are herein incorporated by reference in their entirety.

[0032] Amino-Ether and/or Ester Oxides

[0033] The compositions and methods of the present invention also comprise a safe and effective amount of an amino-ether and/or -ester oxide. Amino-ether and/or -ester oxides according to the invention conform to the formula:



[0034] in which: R_1 is a lower alkyl, R_2 and R_3 which are the same or different are hydrogen or lower alkyl, R_4 is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents which are identical or different, halogen or lower alkoxy, R_5 is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical, Q is —O— or —COO—, n is equal to zero, 1 or 2, m and q are, independently of one another, equal to zero or to 1, p is an integer ranging from 0 to 9.

[0035] By lower radical are meant radicals having from 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, especially 1 to 4 carbon atoms in a straight or branched chain.

[0036] If R_5 is alkyl, it is preferably methyl. If the amino-ether oxides are halogenated, they are preferably brominated or chlorinated.

[0037] The invention also embraces the acid addition salts of amino-ether oxides, notably those of mineral acids, such as halohydrates, sulphates, phosphates, or organic acids such as maleates, citrates, malates, tartrates, methanesulphonates, camphosulphonates, benzoates, etc.

[0038] The invention further covers both racemic and optionally active forms which can be separated, particularly by forming salts with optically active acids.

[0039] Examples of suitable amino-ether and/or -ester oxides include trimebutine (3,4,5-trimethoxybenzoic acid 2-(dimethylamino)-2-phenylbutyl ester), fedotozine ((R)-α-ethyl-N,N-dimethyl-α-[[(3,4,5-trimethoxyphenyl) methoxy]methyl] benzenemethanamine) and mixtures thereof.

[0040] Trimebutine is available under the tradenames Modulon (Canada), Debridat (Italy), Cerekinon (Japan), and Polibutin (Spain). A more detailed description of Fedotozine can be found in U.S. Pat. No. 4,301,163 to Torossian et al. (1981) and U.S. Pat. No. 5,245,080 to Aubard et al. (1993), both of which are herein incorporated by reference in their entirety.

[0041] Fedotozine has been administered effectively at dosages of up to 210 mg daily, preferably 30 to 70 mg three times daily, and up to 100 mg intravenously daily. Trimebutine has been effectively administered orally at up to 600 mg/day, preferably up to 200 milligrams 3 times daily, or intramuscularly/intravenously at up to 100 milligrams every 12 hours. While mindful of individual patient parameters and symptom severity, the amino-ether and/or ester oxides are preferably administered orally at 1-75 mg/kg, preferably 2-50 mg/kg and most preferably at 5-20 mg/kg.

[0042] The compositions of the present invention can additionally contain:

[0043] A. Anti-Inflammatory Agents

[0044] A safe and effective amount of an anti-inflammatory agent may be added to the compositions of the subject invention. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency. A more complete description of the various NSAID's, including acceptable analgesically effective amounts thereof for use in unit dose compositions of the present invention also appears in applicants co-pending U.S. application Ser. Nos. 474,358, filed Mar. 11, 1983, and now U.S. Pat. No. 4,486,436, and 578,288, filed Feb. 8, 1984, now U.S. Pat. No. 4,522,826 the entire disclosures of which are incorporated herein by reference.

[0045] Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionates, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, diflurosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, diflurprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. Mixtures of the above steroidal anti-inflammatory agents can also be used. The preferred steroidal anti-inflammatory for use is hydrocortisone.

[0046] A second class of anti-inflammatory agents which is useful in the compositions includes the nonsteroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology 1, R. A. Scherrer, et al., Academic Press, New York (1974), each incorporated herein by reference.

[0047] Specific non-steroidal anti-inflammatory agents useful in the composition invention include, but are not limited to:

[0048] 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;

[0049] 2) the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;

[0050] 3) the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tol-

metin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac;

[0051] 4) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;

[0052] 5) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and

[0053] 6) the pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

[0054] Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the pharmologically acceptable salts and esters of these agents. For example, etofenamate, a flufenamic acid derivative, is particularly useful for topical application. Of the nonsteroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, etofenamate, aspirin, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, etofenamate, aspirin and flufenamic acid are most preferred.

[0055] Finally, so-called "natural" anti-inflammatory agents are useful in methods of the subject invention. Such agents may suitably be obtained as an extract by suitable physical and/or chemical isolation from natural sources (e.g., plants, fungi, by-products of microorganisms). For example, candelilla wax, alpha bisabolol, aloe vera, Manjistha (extracted from plants in the genus Rubia, particularly *Rubia Cordifolia*), and Guggal (extracted from plants in the genus Commiphora, particularly *Commiphora Mukul*), kola extract, chamomile, and sea whip extract, may be used. Additional anti-inflammatory agents useful herein include compounds of the Licorice (the plant genus/species *Glycyrrhiza glabra*) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof (e.g., salts and esters). Suitable salts of the foregoing compounds include metal and ammonium salts. Suitable esters include C_2-C_{24} saturated or unsaturated esters of the acids, preferably C_{10}-C_{24}, more preferably C_{16}-C_{24}. Specific examples of the foregoing include oil soluble licorice extract, the glycyrrhizic and glycyrrhetic acids themselves, monoammonium glycyrrhizinate, monopotassium glycyrrhizinate, dipotassium glycyrrhizinate, 1-beta-glycyrrhetic acid, stearyl glycyrrhetinate, and 3-stearyloxy-glycyrrhetinic acid, and disodium 3-succinyloxy-beta-glycyrrhetinate. Stearyl glycyrrhetinate is preferred.

[0056] Mixtures of any of the above anti-inflammatory agents can also be used.

[0057] B. Laxatives

[0058] A safe and effective amount of a laxative may be added to the compositions of the subject invention. The exact amount of laxative to be used in the compositions will depend on the particular laxative utilized since such agents vary widely in potency. A more omplete description of the various laxatives, including acceptable laxative effective amounts thereof for use in unit dose compositions of the present invention can be found in U.S. Pat. No. 5,516,524; herein incorporated by reference in its entirety; as well as the Handbook of Nonprescription Drugs, 12th Ed., Chapter 12, pp. 279-290 (American Pharmaceutical Association, Washington, D.C.; 2000); and Drug Facts and Comparisons (54th Ed. 2000), pp. 1166-1177; the cited pages of which are herein incorporated by reference.

[0059] Laxatives useful herein include, but are not limited to, hydrophilic derivatives of cellulose (such methylcellulose and carboxymethylcellulose sodium), malt soup extract, polyacrylic resins (preferably hydrophilic forms such as polycarbophil and calcium polycarbophil), plantago seeds, psyllium husk, dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, dioctyl sodium sulfosuccinate, mineral oil, magnesium citrate, magnesium hydroxide, magnesium sulfate, dibasic sodium phosphate, monobasic sodium phosphate, sodium biphosphate, glycerin, anthraquinones or anthracene laxatives (such as aloe, cascara sagrada, danthron, senna, aloin, casanthranol, frangula, and rhubarb), diphenylmethanes (such as bisacodyl and phenolphthalein), and castor oil. Mixtures of the above laxatives can also be used.

[0060] C. Antidiarrheals

[0061] A safe and effective amount of an antidiarrheal may be added to the compositions of the subject invention. The exact amount of the antidiarrheal to be used in the compositions will depend on the particular antidiarrheal utilized since such agents vary widely in potency. A more complete description of the various antidiarrheals, including acceptable antidiarrheal effective amounts thereof for use in unit dose compositions of the present invention can be found in the Handbook of Nonprescription Drugs, 12th Ed., Chapter 13, pp. 312-316 (American Pharmaceutical Association, Washington, D.C.; 2000); and Drug Facts and Comparisons (54th Ed. 2000), pp. 1178-1182; the cited pages of which are herein incorporated by reference.

[0062] Antidiarrheals useful herein include, but are not limited to, natural or synthetic opiates (such as difenoxin, diphenoxylate, pargoric, opium tincture, and loperamide), anticholinergics (such as belladonna alkoloids—atropine hyoscyamine, and hyosine), acetyltannic acid, albumin tannate, alkofanone, aluminum salicylates, catechin, lidamidine, mebiquine, trillium, and uzarin. Mixtures of the above antidiarrheals can also be used.

[0063] D. Antiulcerative

[0064] A safe and effective amount of an antiulcerative may be added to the compositions of the subject invention. The exact amount of the antiulcerative to be used in the compositions will depend on the particular antiulcerative utilized since such agents vary widely in potency. A more complete description of the various antiulceratives, including acceptable antiulcerative effective amounts thereof for use in unit dose compositions of the present invention can be found in the Drug Facts and Comparisons (54th Ed. 2000), pp. 1131-1139; the cited pages of which are herein incorporated by reference.

[0065] Antiulcerative useful in the present invention include, but are not limited to, aceglutamide aluminum complex, ε-acetamidocaproic acid zinc salt, acetoxolone, arbaprostil, benexate hydrochloride, bismuth subcitrate sol (dried), carbenoxolone, cetraxate, cimetidine, enprostil, esaprazole, famotidine, ftaxilide, gefarnate, guaiazulene,

irsogladine, nizatidine, omeprazole, omoprostil, γ-oryzanol, pifarnine, pirenzepine, plaunotol, ranitidine, rioprostil, rosaprostol, rotraxate, roxatidine acetate, sofalcone, spizofurone, sucralfate, teprenone, trimoprostil, thrithiozine, troxipide, and zolimidine. Mixtures of the above antiulcerative can also be used.

[0066] E. Antibiotics.

[0067] A safe and effective amount of an antibiotic may be added to the compositions of the subject invention. The exact amount of the antibiotic to be used in the compositions will depend on the particular antibiotic utilized since such agents vary widely in potency. A complete description of the various antibiotics, including acceptable antibiotic effective amounts thereof for use in unit dose compositions of the present invention can be found in the Drug Facts and Comparisons (54th Ed. 2000), pp. 1217-1354; the cited pages of which are herein incorporated by reference.

[0068] A wide variety of antibiotics may be used according to the invention, including for example nitroimidazole antibiotics (e.g. tinidazole or metronidazole), tetracyclines (e.g. tetracyclin, doxycyclin and minocyclin), pencillins (e.g. amoxycillin, ampicillin and mezlocillin), cephalosporins (e.g. cefachlor, cefadroxil, cephradine, cefuroxime, cefuroxime axetil, cephalexin, cefpodoxime proxetil, ceftazidime and ceftriaxone), carbopenems (e.g. imipenem and meropenem), amino-glycosides (e.g. paromonycin), macrolide antibiotics (e.g. erythromycin, clarithromycin and azithromycin), lincosamide antibiotics (e.g. clindamycin), 4-quinolones (e.g. ofloxacin, ciprofloxacin, pefloxacin and norfloxacin), rifamycins (e.g. rifampicin), nitrofurantoin and derivatives of 10-(1-hydroxyethyl)-11-oxo-1-azatricyclo [7.2.0.0.3.8]undec-2-ene-2-carboxylic acid and mixtures thereof as well as those described in U.S. Pat. No. 5,719,197 to Kanios et al. (1998), published European Patent Specification No. 0416953 and published International Patent Specification No. WO92/03437, each of which are herein incorporated by reference in its entirety.

[0069] F. Gastric Secretion Inhibitors

[0070] A safe and effective amount of a gastric secretion inhibitor may be added to the compositions of the subject invention. Suitable gastric secretion inhibitors include, but are not limited to, enterogastrone and octreotide. The exact amount of gastric secretion inhibitors to be used in the compositions will depend on the particular gastric secretion inhibitor utilized since such agents vary widely in potency. A more complete description of the various Gastric Secretion Inhibitors, including acceptable e Gastric Secretion Inhibitor effective amounts thereof for use in unit dose compositions of the present invention can be found in the Drug Facts and Comparisons (54th Ed. 2000), pp. 352-354; the cited pages of which are herein incorporated by reference. Mixtures of the above gastric secretion inhibitors can also be used.

[0071] G. Peristaltic Stimulants

[0072] A safe and effective amount of a peristaltic stimulant may be added to the compositions of the subject invention. Suitable peristaltic stimulants include, but are not limited to, dexpanthenol, metoclopromide, cisapride, and domperidone. The exact amount of peristalitc stimulants to be used in the compositions will depend on the particular peristalitc stimulant utilized since such agents vary widely in potency. A more complete description of the various, Peristaltic Stimulants including acceptable Peristaltic Stimulant effective amounts thereof for use in unit dose compositions of the present invention can be found in the Drug Facts and Comparisons (54th Ed. 2000), pp. 1188-1193; the cited pages of which are herein incorporated by reference. Mixtures of the above peristalitc stimulants can also be used.

[0073] H. Serotonin ($5HT_3$) Receptor Antagonist

[0074] A safe and effective amount of a serotonin ($5HT_3$) receptor antagonist may be added to the compositions of the subject invention. Suitable serotonin ($5HT_3$) receptor antagonists include, but are not limited to, cilansetron, dolasetron, ondansetron and alosetron. The exact amount of serotonin ($5HT_3$) receptor antagonists to be used in the compositions will depend on the particular serotonin ($5HT_3$) receptor antagonist utilized since such agents vary widely in potency. A more complete description of the various serotonin ($5HT_3$) receptor antagonists, including acceptable effective amounts thereof for use in unit dose compositions of the present invention can be found in U.S. Pat. No. 6,235,745, herein incorporated by reference and the Drug Facts and Comparisons (54th Ed. 2000), pp. 869-872 and KU47; the cited pages of which are herein incorporated by reference. Mixtures of the above serotonin ($5HT_3$) receptor antagonists can also be used.

[0075] I. Serotonin ($5HT_4$) Receptor Agonist

[0076] A safe and effective amount of a serotonin ($5HT_4$) receptor agonist may be added to the compositions of the subject invention. Suitable serotonin ($5HT_4$) receptor agonists include, but are not limited to tegaserod, renzapride and prucalopride. The exact amount of serotonin ($5HT_4$) receptor agonists to be used in the compositions will depend on the particular serotonin ($5HT_4$) receptor agonist utilized since such agents vary widely in potency. Tegaserod is a partial serotonin ($5HT_4$) receptor agonist which accelerates orocecal transit (without effect on gastic emptying) and tends to enhance colonic transit. 12 mg/day of tegaserod is taught to result in effective relief of irritable bowel syndrome symptoms. Prucalopride is a full serotonin ($5HT_4$) receptor agonist which accelerates gastric, small bowel and colonic transit in functional constipation. Up to 4 mg/day, particularly 2-4 mg/day, of prucalopride is taught to result in effective relief of untoward bowel symptoms. Renzapride possesses both serotonin ($5HT_4$) receptor agonist and serotonin ($5HT_3$) receptor antagonist activity, providing increased gastric emptying and reduced gastrintestinal transit time. Mixtures of the above serotonin ($5HT_4$) receptor agonists can also be used. Mixtures of any of the above-mentioned pharmaceutical compounds can also be used.

[0077] J. Selective Serotonin Reuptake Inhibitors

[0078] A safe and effective amount of a selective serotonin reuptake inhibitor may be added to the compositions of the subject invention. Suitable selective serotonin reuptake inhibitors include, but are not limited to, fluoxetine, fluvoxamine, paroxetine, and sertraline. The exact amount of selective serotonin reuptake inhibitors to be used in the compositions will depend on the particular selective serotonin reuptake inhibitor utilized since such agents vary widely in potency. A more complete description of the various selective serotonin reuptake inhibitors, including acceptable effective amounts thereof for use in unit dose

compositions of the present invention can be found in the Drug Facts and Comparisons (54th Ed. 2000), pp. 918-928; the cited pages of which are herein incorporated by reference. Mixtures of the above selective serotonin reuptake inhibitors can also be used.

[0079] Further dosage information concerning the disclosed actives is summarized in the table below:

Generic Name	Suitable Strengths and Dosage Forms (Brand Names)	Usual Adult Dosage
Bulk-Foaming Laxatives		
Calcium polycarbophil	625-mg tablets that provide 500 mg of polycarbophil (Konsyl Fiber)	1–6 g/day as polycarbophil in divided doses
Methylcellulose	2 g/Tbsp oral powder (Citrucel)	4–6 g/day in divided doses
Psyllium	3.4 g/tsp or 3.4 g/Tbsp oral powder; 1.7 g wafer (Metamucil)	2.5–30 g/day in divided doses
Antidiarrheals (opiate and anticholinergic agents)		
Diphenoxylate	2.5-mg tablets; 2.5 mg/5 mL oral liquid (Lomotil)	2.5–5 mg four times daily as needed for diarrhea
Loperamide	2-mg tablets and capsules; 1 mg/5 mL oral liquid (Imodium)	2–4 mg up to four times daily as needed.
Dicyclomine	10-mg capsules; 20-mg tablets; 10 mg/5 mL syrup (Bentyl)	10–20 mg three or four times daily
Hyoscyamine	0.125-mg tablets; 0.125 mg/mL; 0.125 mg/5 mL elixir (Levsin)	0.15–0.3 mg up to four times daily
Tincture of belladonna	Tincture with 0.3 mg/mL alkaloids of belladonna leaf	0.6–1 mL three or four times daily
Peristaltic Stimulants		
Cisapride	10-, 20-mg tablets; 5 mg/mL oral suspension (Propulsid)	5–10 mg three times daily
Metoclopramide	5-, 10-mg tablets; 5 mg/5 mL oral liquid	
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	20-mg capsules; 20 mg/5 mL oral solution (Prozac)	
Fluvoxamine	50-, 100-mg tablets (Luvox)	
Paroxetine	10 mg/5 mL oral suspension; 10-, 20-, 30-, 40-mg tablets (Paxil)	
Sertraline	25-, 50-, 100-mg tablets (Zoloft)	
Serotonin ($5HT_3$) Receptor Antagonist		
Alosetron	1-mg tablets (Lotronex)	1 mg twice daily
Granisetron	1-mg tablets (Kytril)	
Ondansetron	4-, 8-mg tablets (Zofran)	4 mg three times daily
Gastric Secretion Inhibitors		
Octreotide	50, 100, 200, 500, 1000 μg/mL sterile solution for s.c. or i.v. injection (Sandostatin); 10-, 20-, 30-mg sterile suspensionfor i.m. injection (Sandostatin LAR Depot)	

[0080] Carriers

[0081] In accordance with the practices of the present invention, the gastrointestinal compositions may be administered in admixture with suitable pharmaceutical diluents, carriers or other excipients (collectively referred to as "carrier" materials) suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. The gastrointestinal compositions of the present invention are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The actives can be coadministered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents.

[0082] Examples of suitable tablet or capsule form ingredients, include but are not limited, to oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodiumbenzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc.

[0083] Of course, additionally, the compositions of the present invention may be formulated in sustained release

form to provide the rate controlled release of any one or more of the components to optimize the therapeutic effects, i.e., analgesia, skeletal muscle relaxation, etc. while minimizing undesirable side effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

[0084] Similarly, injectable dosage units may be utilized to accomplish intravenous, intramuscular or subcutaneous administration and, for such parenteral administration, suitable sterile aqueous or non-aqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed.

[0085] Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U.S. Pat. No. 3,903,297 to Robert, issued Sep. 2, 1975, herein incorporated by reference in its entirety. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modem Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976), each of which are herein incorporated by reference in its entirety.

[0086] The gastrointestinal compositions of the present invention may also be formulated and administered by other methods known for administering gastrointestinal actives. For example, the composition may be adapted for topical administration in the form of rectal preparations such as a rectal cream, gel, ointment, or suppository.

[0087] Method of Treatment

[0088] The method of treatment can be any suitable method which is effective in the treatment of the particular type of lower gastrointestinal disorder that is being treated. Treatment may be oral, rectal, parenteral, intravenous administration or injection. The method of applying an effective amount also varies depending on the lower gastrointestinal disorder being treated. It is believed that oral treatment by tablet, capsule or liquid will be the preferred method of administering the compounds to warm blooded mammals.

[0089] The method of treating viral infections may also be by rectal, parenteral, or intravenous administration. The actual time and dosage will depend on the type of the lower gastrointestinal disorder being treated and the desired blood levels.

[0090] In accordance with the practices of the present invention, the gastrointestinal compositions may be administered in admixture with suitable pharmaceutical diluents, carriers or other excipients (collectively referred to as "carrier" materials) suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. The gastrointestinal compositions of the present invention are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The actives can be coadministered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents.

[0091] Examples of suitable tablet or capsule form ingredients, include but are not limited, to oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodiumbenzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc.

[0092] Of course, additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components to optimize the therapeutic effects, i.e., analgesia, skeletal muscle relaxation, etc. while minimizing undesirable side effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

[0093] Similarly, injectable dosage units may be utilized to accomplish intravenous, intramuscular or subcutaneous administration and, for such parenteral administration, suitable sterile aqueous or non-aqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed.

[0094] Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U.S. Pat. No. 3,903,297 to Robert, issued Sep. 2, 1975, herein incorporated by reference in its entirety. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976), each of which are herein incorporated by reference in its entirety.

[0095] The gastrointestinal compositions of the present invention may also be formulated and administered by other

methods known for administering gastrointestinal actives. For example, the composition may be adapted for topical administration in the form of rectal preparations such as a rectal cream, gel, ointment, or suppository.

[0096] Method of Treatment

[0097] The method of treatment can be any suitable method which is effective in the treatment of the particular type of lower gastrointestinal disorder that is being treated. Treatment may be oral, rectal, parenteral, intravenous administration or injection. The method of applying an effective amount also varies depending on the lower gastrointestinal disorder being treated. It is believed that oral treatment by tablet, capsule or liquid will be the preferred method of administering the compounds to warm blooded mammals.

[0098] The method of treating lower gastrointestinal disorders may also be by rectal, parenteral, or intravenous administration. The actual time and dosage will depend on the type of the lower gastrointestinal disorder being treated and the desired blood levels.

EXAMPLES

[0099] The compositions in the following illustrate specific embodiments of the gastrointestinal compositions of the present invention, but are not intended to be limiting thereof. Other modifications can be undertaken by the skilled artisan without departing from the spirit and scope of this invention.

[0100] All exemplified compositions can be prepared by conventional formulation and mixing techniques. Component amounts are listed as weight percents and exclude minor materials such as diluents, filler, and so forth. The listed formulations, therefore, comprise the listed components and any minor materials associated with such components.

Example I

[0101] The following is an example of a gelatin capsule composition of the present invention. The capsule is formed by combining and mixing the ingredients of each column using conventional technology and transferring the mixture to an appropriate sized hard gelatin capsule (e.g., #2 size) for oral administration.

Ingredient	%/w/w
Gabapentin	20.000
Trimebutine	20.000
Lactose NF[1]	5.000
Tricalcium Phosphate[2]	55.000

[1]Lactose NF - Lactose Monohydrate, Amresco Inc.
[2]Tricalcium Phosphate - American International Chemical Inc.

Example II

[0102] The following is an example of a rectal ointment of the present invention.

Ingredient	% w/w
Gabapentin	2.500
Trimebutine	5.000
White Wax NF[1]	5.000
Petrolatum USP[2]	87.500
	100.000

[1]Beeswax, Bleached supplied by Strahl & Pitsch Inc.
[2]White Petrolatum supplied by Witco Corporation

[0103] In a suitable vessel equipped with a heat source and a cover or lid for sealing the vessel, the white wax and petrolatum are added and heated with mixing to a melt temperature of between 85-90° C. C. using a suitable turbine blade agitator. The Gabapentin and Trimebutine are slowly added to the molten petrolatum mixture. The mixture is cooled to a temperature of about 60 degrees C. and then poured into a suitable container.

[0104] The rectal ointment is applied in an appropriate amount (e.g., two to four grams) to the rectal area.

Example III

[0105] The following is an example of an sterile liquid composition of the present invention.

Ingredients	% w/v
Gabapentin	2.500
Trimebutine	1.500
Methyl Paraban[1]	0.020
Water for Injection USP	q.s

[1]Supplied by Universal Preserv-A-Chem, Inc.

[0106] In a suitable vessel, equipped with a suitable turbine agitator, the water for injection is added. While providing moderate agitation, the remaining ingredients are then added and mixed with the water. The mixture is stirred until a homogenous, clear solution is formed. The solution is filtered, aseptically, through a 0.22 micron filter into a sterile container suitable for vial filling. The solution is then aseptically transferred to appropriately sized sterile vials and sealed.

[0107] The injectable is administered hypodermically.

Example IV

[0108] The following is an example of an oral solution of the present invention. The solution is formed by combining and mixing the ingredients of each column using conventional technology and transferring the mixture to an appropriate containers (e.g., HDPE or brown glass). The oral solution is administered orally at dosage amounts of about 5 ml.

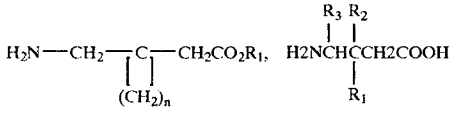
Ingredients	% w/v
Gabapentin	0.025
Trimebutin	0.020
Famotidine	0.002
Alcohol USP (190)[1]	20.000
Purified Water USP	89.955

[1]Ethanol 190 USP, Grain Processing Corporation

What is claimed is:

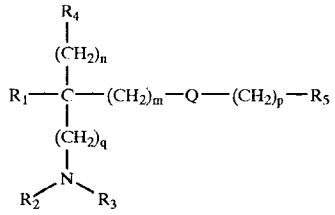
1. A composition for treating or preventing gastrointestinal disorders, comprising:

a) a safe and effective amount of a GABA analog of the formula selected from the group consisting of:



and mixtures thereof; and

b) a safe and effective amount of an amino-ether and/or -ester oxide having the formula:



in which: R_1 is a lower alkyl, R_2 and R_3 which are the same or different are hydrogen or lower alkyl, R_4 is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents which are identical or different, halogen or lower alkoxy, R_5 is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical, Q is —O— or —COO—, n is equal to zero, 1 or 2, m and q are, independently of one another, equal to zero or to 1, p is an integer ranging from 0 to 9.

2. A composition according to claim 1, further comprising an active is selected from the group consisting of antiinflammatory agents, laxatives, antidiarrheals, antibiotics, antiulceratives, gastric secretion inhibitors, peristalitc stimulants, serotonin ($5HT_3$) receptor antagonists, serotonin ($5HT_4$) receptor agonists, selective serotonin reuptake inhibitors and mixtures thereof.

3. A composition according to claim 2, wherein the serotonin ($5HT_4$) receptor agonist is selected from the group consisting of tegaserod, prucalopride and mixtures thereof.

4. A composition according to claim 2, wherein the selective serotonin reuptake inhibitor is selected from the group consising of fluoxetine, fluvoxamine, paroxetine, sertraline and mixtures thereof.

5. A composition according to claim 2, wherein the laxative is selected from the group consisting of methylcellulose, carboxymehylcellulose sodium, malt soup extract, polyacrylic resin, plantago seeds, dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, dioctyl sodium sulfosuccinate, mineral oil, magnesium citrate, magnesium hydroxide, magnesium sulfate, dibasic sodium phosphate, monobasic sodium phosphate, sodium biphosphate, glycerin, anthraquinones, diphenylmethanes, castor oil and mixtures thereof.

6. A composition according to claim 2, wherein the antidiarrheal is selected from the group consisting of natural opiates, synthetic opiates, anticholinergics, acetyltannic acid, albumin tannate, alkofanone, aluminum salicylates, catechin, lidamidine, mebiquine, trillium, uzarin and mixtures thereof.

7. A composition according to claim 2, wherein the antiulcerative is selected from the group consisting of aceglutamide aluminum complex, ϵ-acetamidocaproic acid zinc salt, acetoxolone, arbaprostil, benexate hydrochloride, bismuth subcitrate sol (dried), carbenoxolone, cetraxate, cimetidine, enprostil, esaprazole, famotidine, ftaxilide, gefarnate, guaiazulene, irsogladine, nizatidine, omeprazole, omoprostil, γ-oryzanol, pifarnine, pirenzepine, plaunotol, ranitidine, rioprostil, rosaprostol, rotraxate, roxatidine acetate, sofalcone, spizofurone, sucralfate, teprenone, trimoprostil, thrithiozine, troxipide, zolimidine and mixtures thereof.

8. A composition according to claim 2, wherein the gastric secretion inhibitor is selected from the group consisting of enterogastrone, octreotide and mixtures thereof.

9. A composition according to claim 2, wherein the peristalitc stimulant is selected from the group consisting of metoclopromide, cisapride, domperidone and mixtures thereof.

10. A composition according to claim 2, wherein the serotonin ($5HT_3$) receptor antagonist is selected from the group consisting of renzapride, cilansetron, ondansetron, alosetron and mixtures thereof.

11. A composition according to claim 2, wherein the antibiotic is selected from the group consisting of nitroimidazole antibiotics, tetracyclines, pencillins, cephalosporins, carbopenems, amino-glycosides, macrolide antibiotics, lincosamide antibiotics, 4-quinolones, rifamycins, nitrofurantoin and derivatives of 10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0.3.8]undec-2-ene-2-carboxylic acid and mixtures thereof.

12. A composition according to claim 1, in the form of a tablet, capsule, microcapsule, suspension, solution, injectable, rectal suppository, rectal cream, rectal ointment, rectal gel.

13. A composition according to claim 1, wherein the amino-ether and/or -ester oxide selected from the group consisting of trimebutine, fedotozine and mixtures thereof.

14. A composition according to claim 5, wherein the laxative is a bulk forming laxative.

15. A composition according to claim 14, wherein the laxative is selected from the group consisting of polycarbophil, calcium polycarbophil and mixtures thereof.

16. A composition according to claim 1, in the form of a tablet, capsule, microcapsule, suspension, solution, injectable, rectal suppository, rectal cream, rectal ointment, rectal gel.

17. A composition for treating or preventing gastrointestinal disorders, comprising: a GABA analog selected from the group consisting of (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid, 3-(1-aminoethyl)-5-methylhexanoic acid, 3-aminomethyl-5-methyl-hexanoic acid, and (S)-3-(aminomethyl)-5-methylhexanoic acid and mixtures thereof; and an amino-ether and/or -ester oxide selected from the group consisting of trimebutine, fedotozine and mixtures thereof.

18. A method of treating or preventing gastrointestinal disorders, comprising the step of administering to a mammal in need of such treatment a safe and effective amount of the composition of claim 1.

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(54) **SYNERGISTIC COMBINATIONS**

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(52) **U.S. Cl.** **514/243**; 514/381; 514/561; 514/252.16

(57) **ABSTRACT**

The instant invention relates to a combination of an alpha-2-delta ligand and a PDEV inhibitor for use in therapy, particularly in the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain. Particularly preferred alpha-2-delta ligands are gabapentin and pregabalin. Particularly preferred PDEV inhibitors are sildenafil, vardenafil and tadalafil.

Figure 1.

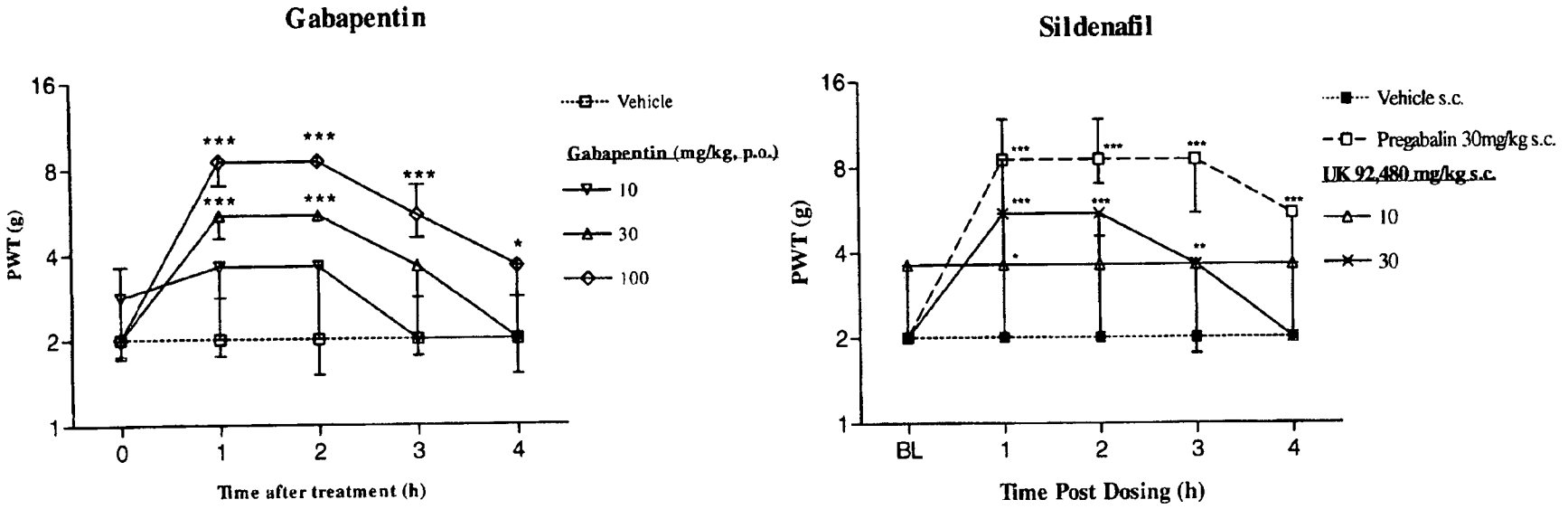
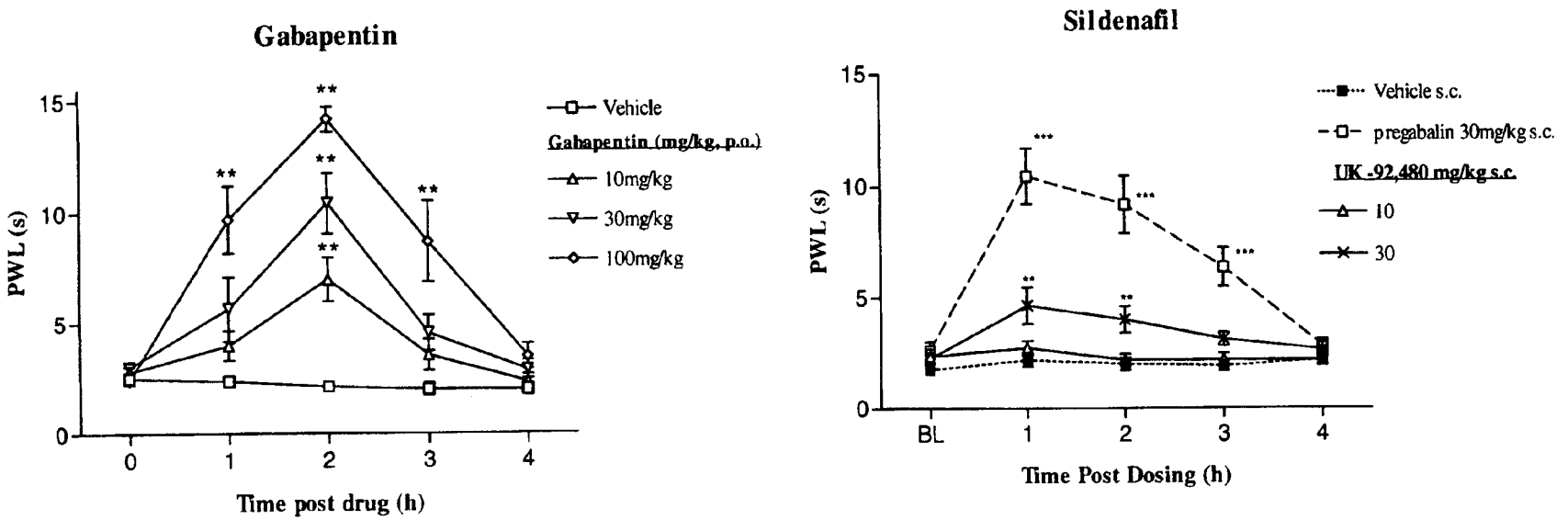

Gabapentin
PWT (g)
16
8
4
2
1
0
1
2
3
4
Time after treatment (h)
***
***
***
***
*
Vehicle
Gabapentin (mg/kg, p.o.)
10
30
100
Sildenafil
PWT (g)
16
8
4
2
1
BL
1
2
3
4
Time Post Dosing (h)
Vehicle s.c.
Pregabalin 30mg/kg s.c.
UK 92,480 mg/kg s.c.
10
30

Figure 2.


Gabapentin
PWL (s)
15
10
5
0
0
1
2
3
4
Time post drug (h)
**
Vehicle
Gabapentin (mg/kg, p.o.)
10mg/kg
30mg/kg
100mg/kg
Sildenafil
PWL (s)
15
10
5
0
BL
1
2
3
4
Time Post Dosing (h)
***
Vehicle s.c.
pregabalin 30mg/kg s.c.
UK-92,480 mg/kg s.c.
10
30

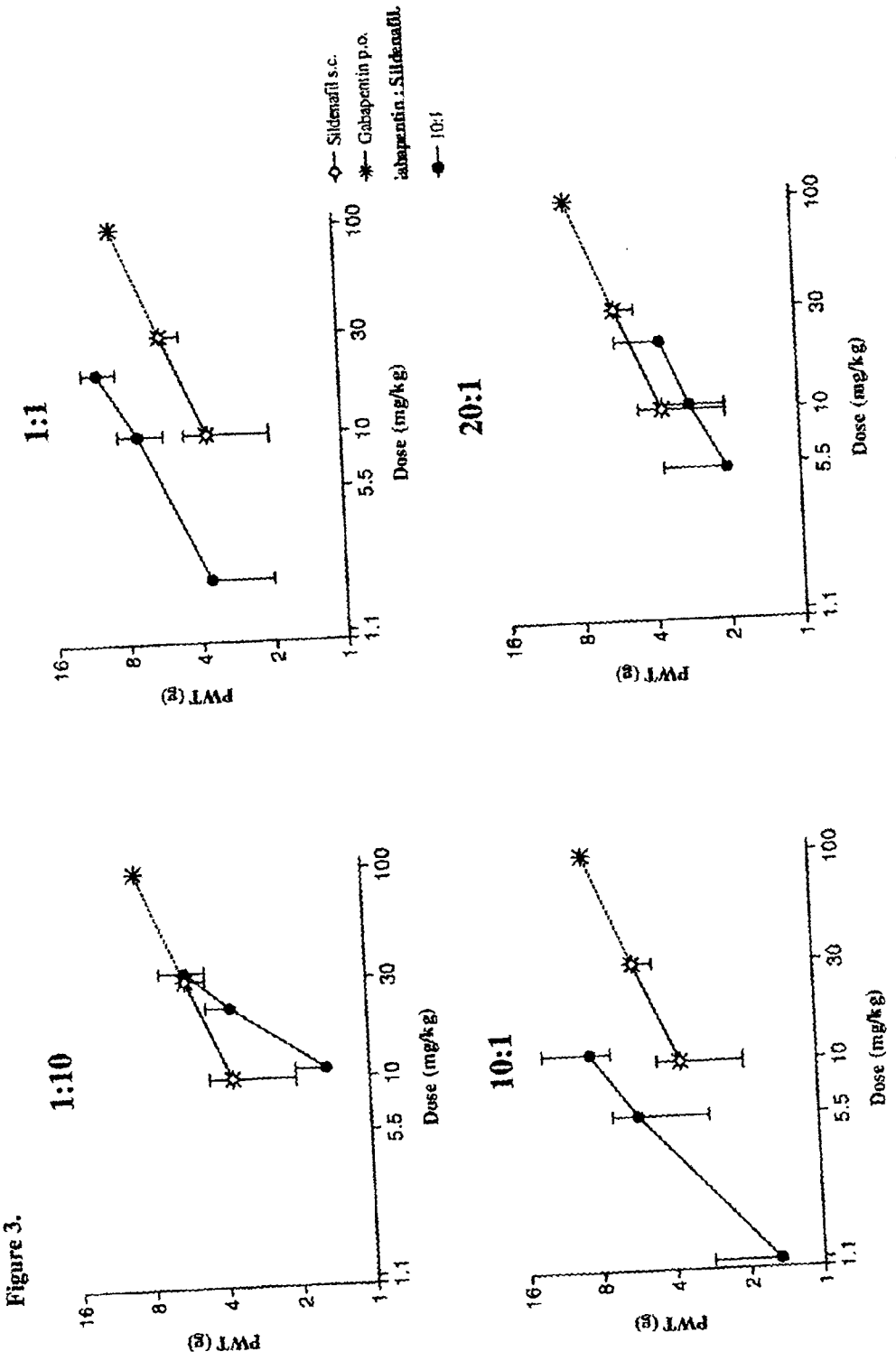
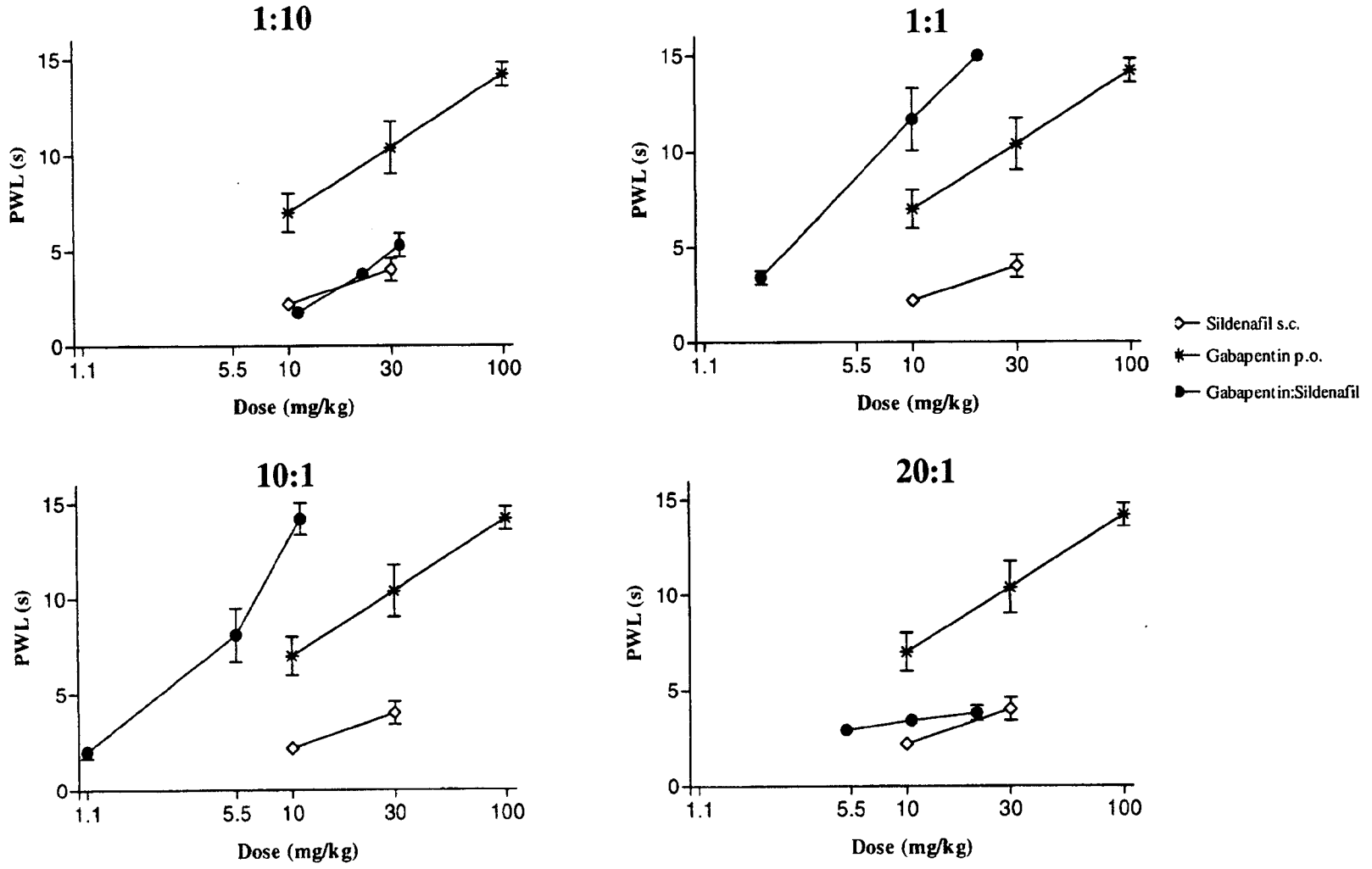

1:1
1:10
20:1
10:1
PWT (g)
Dose (mg/kg)
16
8
4
2
1
1.1
5.5
10
30
100
Sildenafil s.c.
Gabapentin p.o.
Gabapentin : Sildenafil
10:1

Figure 3.

Figure 4.


1:10
1:1
10:1
20:1
PWL (s)
Dose (mg/kg)
0
5
10
15
1.1
5.5
10
30
100
Sildenafil s.c.
Gabapentin p.o.
Gabapentin:Sildenafil

SYNERGISTIC COMBINATIONS

[0001] This U.S. Utility Application claims the benefit of United Kingdom Application Number 0219024.7 filed Aug. 15, 2002 and U.S. Provisional Application No. 60/411,493 filed Sep. 16, 2002.

FIELD OF THE INVENTION

[0002] This invention relates to combinations of an alpha-2-delta ligand and a cGMP PDEV ('PDEV') inhibitor, particularly those which exhibit a synergistic effect, particularly for the curative, prophylactic or palliative treatment of pain and related disorders.

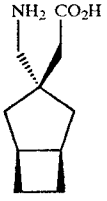
BACKGROUND TO THE INVENTION

[0003] Alpha-2-delta ligands may be defined as compounds which selectively displace ^{3}H-gabapentin from porcine brain membranes indicating a high affinity interaction with the alpha-2-delta ($\alpha_2\delta$) subunit of voltage-gated calcium channels. Alpha-2-delta ligands also includes compounds which do not displace ^{3}H-gabapentin, but are structurally similar to compounds that do, which might be expected to bind alpha-2-delta at a slightly different site than ^{3}H-gabapentin or may bind to human brain alpha-2-delta but not porcine alpha-2-delta. They may also be known as GABA analogs.

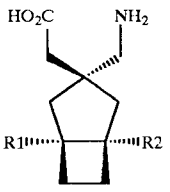
[0004] Alpha-2-delta ligands have been described for a number of indications. The best known alpha-2-delta ligand, gabapentin (NEURONTIN®), 1-(aminomethyl)-cyclohexylacetic acid, was first described in the patent literature in the patent family comprising U.S. Pat. No. 4,024,175. The compound is approved for the treatment of epilepsy and neuropathic pain.

[0005] A second alpha-2-delta ligand, pregabalin, (S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid, is described in European patent application publication number EP641330 as an anti-convulsant treatment useful in the treatment of epilepsy and in EP0934061 for the treatment of pain.

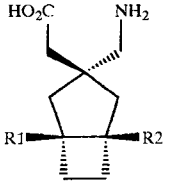
[0006] Further WO0128978, describes a series of alpha-2-delta ligands, particularly (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, depicted below:



[0007] More recently, International Patent Application Number PCT/IB02/01146 (unpublished at the priority date of the present invention) and published as WO02/085839, describes a series of alpha-2-delta ligands of the following formulae:



(I)



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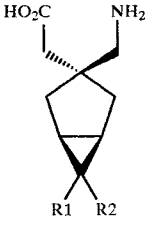

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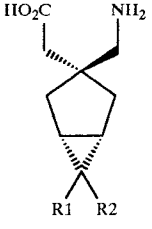

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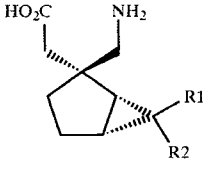

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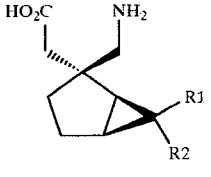

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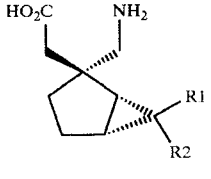

(VII)

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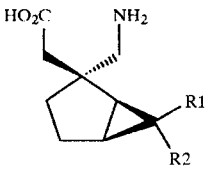
(VIII)



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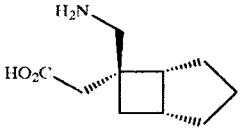

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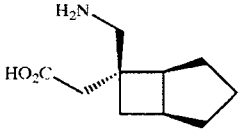

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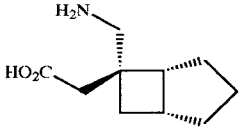

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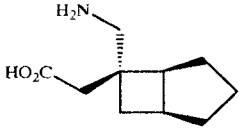

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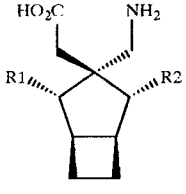

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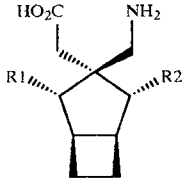

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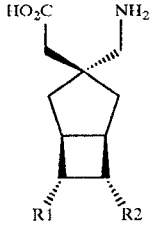

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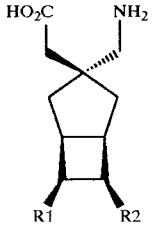

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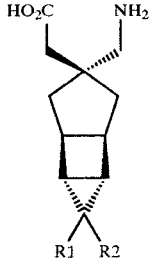

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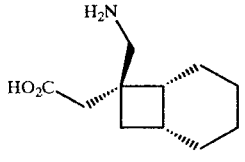

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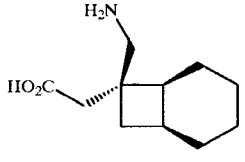

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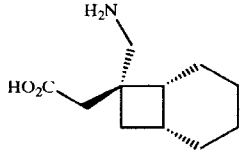
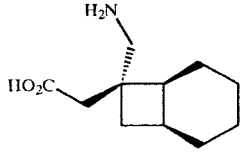


XXI



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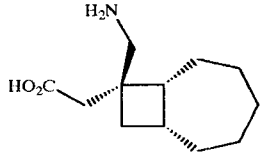

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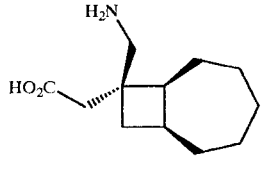

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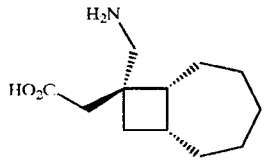

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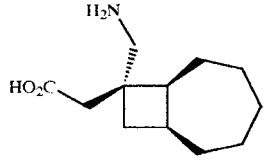
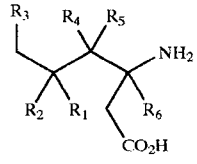


[0008] wherein R^1 and R^2 are each independently selected from H, straight or branched alkyl of 1-6 carbon atoms, cycloalkyl of from 3-6 carbon atoms, phenyl and benzyl, subject to the proviso that, except in the case of a tricyclooctane compound of formula (XVII), R^1 and R^2 are not simultaneously hydrogen; for use in the treatment of a number of indications, including pain.

[0009] International Patent application No. PCT/IB03/00976, unpublished at the filing date of the present invention, describes compounds of the formula I, below:

(I)



[0010] wherein R_1 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with from one to five fluorine atoms;

[0011] R_2 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with from one to five fluorine atoms; or

[0012] R_1 and R_2, together with the carbon to which they are attached, form a three to six membered cycloalkyl ring;

[0013] R_3 is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl-$(C_1$-$C_3)$alkyl, phenyl, phenyl-$(C_1$-$C_3)$alkyl, pyridyl, pyridyl-$(C_1$-$C_3)$alkyl, phenyl-N(H)—, or pyridyl-N(H)—, wherein each of the foregoing alkyl moieties can be optionally substituted with from one to five fluorine atoms, preferably with from zero to three fluorine atoms, and wherein said phenyl and said pyridyl and the phenyl and pyridyl moieties of said phenyl-$(C_1$-$C_3)$alkyl and said pyridyl-$(C_1$-$C_3)$alkyl, respectively, can be optionally substituted with from one to three substituents, preferably with from zero to two substituents, independently selected from chloro, fluoro, amino, nitro, cyano, $(C_1$-$C_3)$alkylamino, $(C_1$-$C_3)$alkyl optionally substituted with from one to three fluorine atoms and $(C_1$-$C_3)$alkoxy optionally substituted with from one to three fluorine atoms;

[0014] R_4 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with from one to five fluorine atoms;

[0015] R_5 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with from one to five fluorine atoms; and

[0016] R_6 is hydrogen or $(C_1$-$C_6)$alkyl;

[0017] and the pharmaceutically acceptable salts of such compounds.

[0018] Inhibitors of the cyclic guanosine 3', 5'-monophosphate phosphodiesterase type five (cGMP PDEV) enzyme ('PDEV inhibitors') may be characterized by compounds with high affinity and selectivity for the PDEV enzyme with little or no affinity for the other phosphodiesterase isoforms and they have been described as being useful for treating a number of indications. In particular, sildenafil (5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one) (VIAGRA®) has been described for the treatment of a number of cardiovascular disorders and has proved to be successful as the first orally effective treatment for male erectile dysfunction (MED). The use of PDEV inhibitors in the treatment of neuropathy has been described in European Patent Application Number EP1129706 and WO01/26659. Analgesic effects of sildenafil have recently been described in Jain et al, Brain Research, 909, 170-178 (2001); Asomoza-Espinosa et al, Eur. J. Pharm., 418, 195-200 (2001); and Mixcoatl-Zecutal et al, Eur. J. Pharm., 400, 81-87 (2001).

SUMMARY OF THE INVENTION

[0019] It has now been found that combination therapy with an alpha-2-delta ligand and a PDEV inhibitor results in unexpected improvement in the treatment of pain. When administered simultaneously, sequentially or separately, the alpha-2-delta ligand and PDEV inhibitor interact in a synergistic manner to control pain. This unexpected synergy allows a reduction in the dose required of each compound, leading to a reduction in the side effects and enhancement of the clinical effectiveness of the compounds and treatment.

[0020] Accordingly, as a first aspect, the invention provides a combination product comprising an alpha-2-delta ligand, excluding pregabalin and gabapentin, and a PDEV inhibitor. Alternatively, the exclusion may also include the compounds (i)-(xxv) of PCT/IB02/01146.

[0021] As an alternative or further aspect, the invention provides a synergistic combination product comprising an alpha-2-delta ligand and a PDEV inhibitor.

[0022] Examples of alpha-2-delta ligands for use with the present invention are those compounds generally or specifically disclosed in U.S. Pat. No. 4,024,175, particularly gabapentin, EP641330, particularly pregabalin, U.S. Pat. No. 5,563,175, WO9733858, WO9733859, WO9931057, WO9931074, WO9729101, WO02085839, particularly [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0.]hept-6-yl]acetic acid, WO9931075, particularly 3-(1-Aminomethyl-cyclohexylmethyl)-

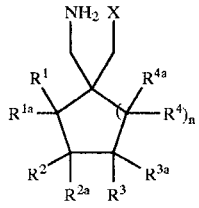
[0023] 4H-[1,2,4]oxadiazol-5-one and C-[1-(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, WO9921824, particularly (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, WO0190052, WO0128978, particularly (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic

acid, EP0641330, WO9817627, WO0076958, particularly (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, PCT/IB03/00976, particularly (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-Amino-5-methyl-octanoic acid, EP1178034, EP1201240, WO9931074, WO03000642, WO0222568, WO0230871, WO0230881, WO02100392, WO02100347, WO0242414, WO0232736 and WO0228881, and pharmaceutically acceptable salts and solvates thereof, all of which are incorporated herein by reference.

[0024] Preferred alpha-2-delta ligands of the present invention include: gabapentin, pregabalin, [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one and C-[1-(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-Aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-Amino-5-methyl-octanoic acid.

[0025] Useful cyclic alpha-2-delta ligands of the present invention may be depicted by the following formula (I):

(I)



[0026] wherein X is a carboxylic acid or carboxylic acid bioisostere;

[0027] n is 0, 1 or 2; and

[0028] R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, R^4 and R^{4a} are independently selected from H and C_1-C_6 alkyl, or

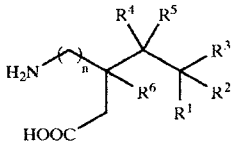
[0029] R^1 and R^2 or R^2 and R^3 are taken together to form a C_3-C_7 cycloalkyl ring, which is optionally substituted with one or two substituents selected from C_1-C_6 alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0030] In formula (I), suitably, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 are independently selected from H and methyl, or R^{1a}, R^{2a}, R^{3a} and R^{4a} are H and R^1 and R^2 or R^2 and R^3 are taken together to form a C_3-C_7 cycloalkyl ring, which is optionally substituted with one or two methyl substituents. A suitable carboxylic acid bioisostere is selected from tetrazolyl and oxadiazolonyl. X is preferably a carboxylic acid.

[0031] In formula (I), preferably, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 are independently selected from H and methyl, or R^{1a}, R^{2a}, R^{3a} and R^{4a} are H and R^1 and R^2 or R^2 and R^3 are taken together to form a C_4-C_5 cycloalkyl ring, or, when n is 0, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 form a cyclopentyl ring, or, when n is 1, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 are both methyl or R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 form a cyclobutyl ring, or, when n is 2, R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, R^4 and R^{4a} are H, or, n is 0, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 form a cyclopentyl ring.

[0032] Useful acyclic alpha-2-delta ligands of the present invention may be depicted by the following formula (II):

(II)



[0033] wherein:

[0034] n is 0 or 1, R^1 is hydrogen or (C_1-C_6)alkyl; R^2 is hydrogen or (C_1-C_6)alkyl; R^3 is hydrogen or (C_1-C_6)alkyl; R^4 is hydrogen or (C_1-C_6)alkyl; R^5 is hydrogen or (C_1-C_6)alkyl and R^2 is hydrogen or (C_1-C_6)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0035] According to formula (II), suitably R^1 is C_1-C_6 alkyl, R^2 is methyl, R^3-R^6 are hydrogen and n is 0 or 1. More suitably R^1 is methyl, ethyl, n-propyl or n-butyl, R^2 is methyl, R^3-R^6 are hydrogen and n is 0 or 1. When R^2 is methyl, R^3-R^6 are hydrogen and n is 0, R^1 is suitably ethyl, n-propyl or n-butyl. When R^2 is methyl, R^3 -R^6 are hydrogen and n is 1, R^1 is suitably methyl or n-propyl. Compounds of formula (II) are suitably in the 3S,5R configuration.

[0036] Examples of PDEV inhibitors for use with the invention are: the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0463756; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0526004; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 93/06104; the isomeric pyrazolo [3,4d] pyrimidin-4-ones disclosed in published international patent application WO 93/07149; the quinazolin-4-ones disclosed in published international patent application WO 93/12095; the pyrido [3,2-d]pyrimidin-4-ones disclosed in published international patent application WO 94/05661; the purin-6-ones disclosed in published international patent application WO 94/00453; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 98/49166; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 99/54333; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995 751; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 00/24745; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995750; the hexahydropyrazino [2',1':6,1]pyrido [3,4-b] indole-1,4-diones disclosed in published international application WO95/19978; the imidazo[5,1-f][1,2,4]triazin-ones disclosed in EP-A-1092719 and in published international application WO 99/24433 and the bicyclic compounds disclosed in published international application WO 93/07124, all of which are incorporated herein by reference.

[0037] Further examples of suitable PDEV inhibitors for use herein include: the pyrazolo [4,3-d]pyrimidin-7-ones

disclosed in published international application WO 01/27112; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27113; the compounds disclosed in EP-A-1092718 and the compounds disclosed in EP-A-1092719; the tricyclic compounds disclosed in EP-A-1241170; the alkyl sulphone compounds disclosed in published international application WO 02/074774; the compounds disclosed in published international application WO 02/072586; the compounds disclosed in published international application WO 02/079203 and the compounds disclosed in WO 02/074312, all of which are incorporated herein by reference.

[0038] Yet further examples of suitable PDEV inhibitors for use herein include: the carboline derivatives described in WO03000691, WO02098875, WO02064591, WO02064590 and WO0108688, the pyrazino [1',2':1,6] pyrido [3,4-B] indole 1,4-dione derivatives described in WO02098877, the tetracyclic compounds described in WO02098428, the compounds described in WO02088123 and WO0200656, the condensed pyrazindione derivatives described in WO0238563 and WO02000657, the indole derivatives described in WO0236593, the condensed pyrindole derivatives described in WO0228865 and WO0228859, the hexahydropyrazino[1',2':1,6]-pyrido [3,4-B] indole-1,4-dione derivatives described in WO0228858 and WO0194345, the fused heterocyclic derivatives described in WO0210166, the cyclic GMP specific phosphodiesterase inhibitors described in WO0200658, the tetracyclic diketopiperazine compounds described in WO0194347 and the compounds described in use application WO0219213, all of which are incorporated herein by reference.

[0039] Still other PDEV inhibitors inhibitors useful in conjunction with the present invention include: 4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amiono]-6-chloro-2-quinozolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cylopent-4,5] imidazo[2,1-b]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]-imidazo [2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl) propoxy)-3-(2H)pyridazinone; 1-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)arnino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 (Eisai); Bay-38-3045 & 38-9456 (Bayer); FR229934 and FR226807 (Fujisawa); and Sch-51866.

[0040] Preferred PDEV inhibitors for the use according to the present invention include:

[0041] (i) 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756);

[0042] (ii) 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see EP-A-0526004);

[0043] (iii) 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/49166);

[0044] (iv) 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333);

[0045] (v) (+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one, also known as 3-ethyl-5-{5-[4-ethylpiperazin-1-ylsulphonyl]-2-([(1R)-2-methoxy-1-methylethyl]oxy)pyridin-3-yl}-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333);

[0046] (vi) 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulphonyl}-4-ethylpiperazine (see WO 01/27113, Example 8);

[0047] (vii) 5-[2-iso-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 15);

[0048] (viii) 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 66);

[0049] (ix) 5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27112, Example 124);

[0050] (x) 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27112, Example 132);

[0051] (xi) (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (tadalafil, IC-351, Cialis®), i.e. the compound of examples 78 and 95 of published international application WO95/19978, as well as the compound of examples 1, 3, 7 and 8;

[0052] (xii) 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7propyl-3H-imidazo [5,1-f][1,2,4]traizin-4-one (vardenafil) also known as 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulphonyl]-4-ethylpiperazine, i.e. the compound of examples 20, 19, 337 and 336 of published international application WO99/24433;

[0053] (xiii) the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in WO00/27848, in particular N-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-

d]-pyrimidin-5-yl)-4-propxyphenyl]sulfonyl]-1-methyl2-pyrrolidinepropanamide [DA-8159 (Example 68 of WO00/27848)];

[0054] (xiv) the compound of example 11 of published international application WO093/07124;

[0055] (xv) 4-(4-chlorobenzyl)amino-6,7,8-trimethoxyquinazoline; and

[0056] (xvi) 7,8-dihydro-8-oxo-6-[2-propoxyphenyl]-1H-imidazo[4,5-g]quinazoline;

[0057] (xvii) 1-[3-[1-[(4-fluorophenyl)methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propozyphenyl]carboxamide;

[0058] (xviii) 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

[0059] (xix) 1- {6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine; and pharmaceutically acceptable salts and solvates thereof.

[0060] The suitability of any particular PDEV inhibitor can be readily determined by evaluation of its potency and selectivity using literature methods followed by evaluation of its toxicity, absorption, metabolism, pharmacokinetics, etc in accordance with standard pharmaceutical practice.

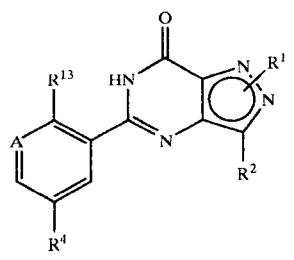
[0061] Preferably, the PDEV inhibitors have an IC_{50} at less than 100 nanomolar, more preferably, at less than 50 nanomolar, more preferably still at less than 10 nanomolar.

[0062] IC50 values for the PDEV inhibitors may be determined using the PDE5 assay described hereinafter.

[0063] Preferably the PDEV inhibitors used in the pharmaceutical combinations according to the present invention are selective for the PDEV enzyme. Preferably they have a selectivity of PDEV over PDE3 of greater than 100 more preferably greater than 300. More preferably the PDEV inhibitor has a selectivity over both PDE3 and PDE4 of greater than 100, more preferably greater than 300. Selectivity ratios may readily be determined by the skilled person. IC50 values for the PDE3 and PDE4 enzyme may be determined using established literature methodology, see S A Ballard et al, Journal of Urology, 1998, vol. 159, pages 2164-2171 and as detailed herein after.

[0064] Useful PDEV inhibitors of the present invention may be depicted by the following formula (III):

(III)



[0065] wherein:

[0066] A is CH or N;

[0067] R^1 is H, C_1 to C_6 alkyl, C_3 to C_6 alkenyl, C_3 to C_6 cycloalkyl, C_3 to C_6 cycloalkenyl, or C_1-C_3 perfluoroalkyl, wherein said alkyl group may be branched or straight chain and wherein said alkyl, alkenyl, cycloalkyl or perfluoroalkyl group is optionally substituted by; one or more substituents selected from: hydroxy; C_1 to C_4 alkoxy; C_3 to C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; phenyl substituted with one or more substitutents selected from C_1 to C_3 alkyl, C_1 to C_4 alkoxy, C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy wherein said haloalkyl and haloalkoxy groups contain one or more halo atoms, halo, CN, NO_2, NHR^{11}, $NHSO_2R^{12}$, SO_2R^{12}, SO_2NHR^{11}, COR^{11}, CO_2R^{11} wherein R^{11} is H, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, C_1 to C_4 alkanoyl, $C_1$to C_4 haloalkyl or C_1 to C_4 haloalkoxy and wherein R^{12} is C_1 to C_4 alkyl, C_2 to C_4 alkenyl, C_1 to C_4 alkanoyl, C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy; NR^7R^8, $CONR^7R^8$ or NR^7COR^{11} wherein R^7 and R^8 are each independently selected from H, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, C_1 to C_4 alkoxy, CO_2R^9, SO_2R^9 wherein said alkyl, alkenyl or alkoxy groups are optionally substituted by NR^5R^6, C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy and wherein R^9 is H, hydroxy C_2 to C_3 alkyl, C_1 to C_4 alkanoyl or C_1 to C_4 alkyl which is optionally substituted with phenyl wherein said phenyl group is optionally substituted by one or more substituents selected from C_1 to C_4 alkyl optionally substituted by C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy, C_1 to C_4 alkoxy, halo, CN, NO_2, NHR^{11}, $NHSO_2R^{12}$, SO_2R^{12}, SO_2NHR^{11}, COR^{11} or CO_2R^{11}; Het^1; Het^2 or Het^3; or R^1 is Het^4 or phenyl wherein said phenyl group is optionally substituted by one or more substituents selected from C_1 to C_4 alkyl, C_2 to C_4 alkenyl, C_1 to C_4 alkoxy, halo, CN, CF_3, OCF_3, NO_2, NHR^{11}, $NHSO_2R^{12}$, SO_2R^{12}, SO_2NHR^{11}, COR^{11}, CO_2R^{11};

[0068] R^2 is H, C_1 to C_6 alkyl, C_3 to C_6 alkenyl or $(CH_2)_n$(C_3 to C_6 cycloalkyl) wherein n is 0, 1 or 2 and wherein said alkyl or alkyenyl group is optionally substituted with one or more fluoro substituents;

[0069] R^{13} is OR^3 or NR^5R^6;

[0070] R^3 is C_1 to C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, C_1-C_6 perfluoroalkyl or (C_3-C_6 cycloalkyl)C_1-C_6 alkyl optionally substituted with one or two substituents selected from C_3 to C_5 cycloalkyl, hydroxy, C_1 to C_4 alkoxy, C_3-C_6 alkenyl, C_3-C_6 alkynyl, benzyloxy, NR^5R^6, phenyl, Het^1, Het^2, Het^3 or Het^4 wherein the C_1 to C_6 alkyl and C_1 to C_4 alkoxy groups may optionally be terminated by a haloalkyl group such as CF_3; C_3 to C_6 cycloalkyl; Het^1, Het^2, Het^3 or Het^4;

[0071] R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; hydroxy C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7;

halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or phenyl or heterocyclyl either of which is optionally substituted with methyl; or R^4 is a pyrrolidinylsulphonyl, piperidinosulphonyl, morpholinosulphonyl, or piperazin-1-ylsulphonyl group having a substituent, R^{10} at the 4-position of the piperazinyl group wherein said piperazinyl group is optionally substituted with one or two C_1 to C_4 alkyl, C_1 to C_3 alkoxy, NR^7R^8 or CON R^7R^8 groups and is optionally in the form of its 4-N-oxide;

[0072] R^5 and R^6 are each independently selected from H and C_1 to C_4 alkyl optionally substituted with C_3 to C_5 cycloalkyl or C_1 to C_4 alkoxy, or, together with the nitrogen atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 4-(NR^9)- piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;

[0073] R^{10} is H; C_1 to C_6 alkyl, (C_1-C_3 alkoxy) C_2-C_6 alkyl, hydroxy C_2-C_6 alkyl, (R^7R^8N)C_2-C_6 alkyl, (R^7R^8NCO)C_1-C_6 alkyl, $CONR^7R^8$, $CSNR^7R^8$ or C(NH)NR^7R^8 optionally substituted with one or two substituents selected from hydroxy, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with C_1 to C_4 alkyl or C_1 to C_4 alkoxy; C_2 to C_6 alkenyl or Het^4;

[0074] Het^1 is an N-linked 4-, 5- or 6-membered nitrogen-containing heterocyclic group optionally containing one or more further heteroatoms selected from S, N or O;

[0075] Het^2 is a C-linked 5-membered heterocyclic group containing an O, S or N heteroatom optionally containing one or more heteroatoms selected from O or S;

[0076] Het^3 is a C-linked 6-membered heterocyclic group containing an O or S heteroatom optionally containing one or more heteroatoms selected from O, S or N or Het^3 is a C-linked 6-membered heterocyclic group containing three N heteroatoms;

[0077] Het^4 is a C-linked 4-, 5- or 6-membered heterocyclic group containing one, two or three heteroatoms selected from S, O or N; and wherein any of said heterocyclic groups Het^1, Het^2, Het^3 or Het^4 may be saturated, partially unsaturated or aromatic and wherein any of said heterocyclic groups may be optionally substituted with one or more substituents selected from C_1 to C_4 alkyl, C_2 to C_4 alkenyl, C_1 to C_4 alkoxy, halo, CO_2R^{11}, COR^{11}, SO_2R^{12} or NHR^{11} and/or wherein any of said heterocyclic groups is benzo-fused;

[0078] or wherein when R^{13} represents OR^3 or R^3NR^5; R^1 represents Het, alkylHet, aryl or alkylaryl, which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$; R^2 represents H, halo, cyano, nitro, OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$, lower alkyl, Het, alkylhet, aryl or alkylaryl, which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$; R^3 represents H, lower alkyl, alkylHet or alkylaryl, which latter three groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$; R^4 represents H, halo, cyano, nitro, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $NR^{16}Y(O)R^{17}$, SOR^{18}, $SO_2R^{19}R^{20}$, C(O)AZ, lower alkyl, lower alkenyl, lower alkynyl, Het, alkylHet, aryl, alkylaryl, which latter seven groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}OR^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$; Y represents C or S(O), wherein one of R^{16} and R^{17} is not present when Y is S(O); A represents lower alkylene; Z represents OR^6, halo, Het or aryl, which latter two groups are both optionally substituted with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$; R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19} and R^{20} independently represent H or lower alkyl; R^{10} and R^{11} independently represent H or lower alkyl, which latter group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$ or Het or aryl optionally substituted with one or more of said latter eleven groups or one of R^{10} and R^{11} may be lower alkoxy, amino or Het, which latter two groups are both optionally substituted with lower alkyl; R^{12} and R^{13} independently represent H or lower alkyl or one of R^{12} or R^{13} may be C(O)-lower alkyl or C(O)Het in which Het is optionally substituted with lower alkyl; R^{14} and R^{15} independently represent H or lower alkyl or R^{14} and R^{15}, together with the nitrogen atom to which they are bound, form a heterocyclic ring; R^{16} and R^{17} independently represent H or lower alkyl or one of R^{16} and R^{17} may be Het or aryl, which latter two groups are both optionally substituted with lower alkyl; Het represents an optionally substituted four to twelve membered heterocyclic group, which may be aromatic or non-aromatic, which may contain one or more double bonds, which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, S and O; or a pharmaceutically acceptable salt or solvate of any thereof.

[0079] In formula (III), the PDEV inhibitor may contain halo groups. Here, "halo" means fluoro, chloro, bromo or iodo.

[0080] In formula (III), the PDE5 inhibitor may contain one or more of alkyl, alkoxy, alkenyl, alkylene and alkenylene groups—which may be unbranched- or branched-chain.

[0081] In formula (III), a preferred group of compounds for use according to the present invention are those wherein: R^1 is H, methyl or ethyl; R^2 is H, C_1-C_3 alkyl optionally substituted by OH, or methoxy; R^3 is C_2-C_3 alkyl or allyl; R^4 is a sulphonylpiperidino or 4-N—(R^{10})-sulphonylpiperazin-1-yl group; R^5 is H, NR^7R^8, or $CONR^7R^8$; R^{10} is H, C_1-C_3 alkyl, hydroxy C_2-C_6 alkyl, $CONR^7R^8$, $CSNR^7R^8$ or $C(NH)NR^7R^8$; R^7 and R^8 are each independently H or methyl.

[0082] In formula (III), another preferred group of compounds for use according to the present invention are those wherein: R^1 is C_1 to C_2 alkyl optionally substituted with Het; 2-(morpholin-4-yl)ethyl or benzyl; R^2 is C_2 to C_4 alkyl; R^{13} is OR^3 or NR^5R^6; R^3 is C_1 to C_4 alkyl optionally substituted with one or two substituents selected from cyclopropyl, cyclobutyl, OH, methoxy, ethoxy, benzyloxy, NR^5R^6, phenyl, furan-3-yl, pyridin-2-yl and pyridin-3-yl; cyclobutyl; 1-methylpiperidin-4-yl; tetrahydrofuran-3-yl or tetrahydropyran-4-yl; R^5 and R^6 are each independently selected from H and C_1 to C_2 alkyl optionally substituted with cyclopropyl or methoxy, or, together with the nitrogen atom to which they are attached, form a azetidinyl, pyrrolidinyl or morpholinyl group; R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally substituted with one or two methyl groups and optionally in the form of its 4-N-oxide; R^{10} is H, C_1 to C_3 alkyl optionally substituted with one or two substituents selected from OH, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with methoxy, benzodioxol-5-yl and benzodioxan-2-yl; allyl; pyridin-2-yl; pyridin-4-yl or pyrimidin-2-yl; and Het is selected from pyridin-2-yl; 1-oxidopyridin-2-yl; 6-methylpyridin-2-yl; 6-methoxypyridin-2-yl; pyridazin-3-yl; pyrimidin-2-yl and 1-methylimidazol-2-yl. Of this group more preferred are those compounds wherein R^1 is C_1 to C_2 alkyl optionally substituted with Het; 2-(morpholin-4-yl)ethyl or benzyl; R^2 is C_2 to C_4 alkyl; R^{13} is OR^3; R^3 is C_1 to C_4 alkyl optionally monosubstituted with cyclopropyl, cyclobutyl, OH, methoxy, ethoxy, phenyl, furan-3-yl or pyridin-2-yl; cyclobutyl; tetrahydrofuran-3-yl or tetrahydropyran-4-yl; R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally in the form of its 4-N-oxide; R^{10} is C_1 to C_3 alkyl optionally monosubstituted with OH; and Het is selected from pyridin-2-yl; 1-oxidopyridin-2-yl; 6-methylpyridin-2-yl; 6-methoxypyridin-2-yl; pyridazin-3-yl; pyrimidin-2-yl and 1-methylimidazol-2-yl.

[0083] In formula (III), one other further preferred group of compounds for use according to the present invention are those wherein: R^1 is C_1 to C_6 alkyl or C_3 to C_6 alkenyl wherein said alkyl or alkenyl groups may be branched chain or straight chain or R^1 is C_3 to C_6 cycloalkyl or C_4 to C_6 cycloalkenyl and wherein when R^1 is C_1 to C_3 alkyl said alkyl group is substituted by; and wherein when R^1 is C_4 to C_6 alkyl, C_3 to C_6 alkenyl, C_3 to C_6 cycloalkyl or C_4 to C_6 cycloalkenyl said alkyl, alkenyl, cycloalkyl or cycloalkenyl group is optionally substituted by; one or more substituents selected from: hydroxy; C_1 to C_4 alkoxy; C_3 to C_4 cycloalkyl; phenyl substituted with one or more substitutents selected from C_1 to C_3 alkyl, C_1 to C_4 alkoxy, C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy, halo, CN, NO_2, NHR^{11}, $NHCOR^{12}$, $NHSO_2R^{12}$, SO_2R^{12}, SO_2NHR^{11}, COR^{11}, CO^2R^{11} wherein said haloalkyl and haloalkoxy groups contain one or more halo atoms; NR^7R^8, $CONR^7R^8$ or NR^7COR^{11}; a Het^1 group which is an N-linked 4-membered N-containing heterocyclic group; a Het^2 group which is a C-linked 5-membered heterocyclic group containing an O, S or N heteroatom optionally containing one or more heteroatoms selected from N, O or S; a Het^3 group which is a C-linked 6-membered heterocyclic group containing an O or S heteroatom optionally containing one or more heteroatoms selected from O, S or N or a Het^3 group which is a C-linked 6-membered heterocyclic group containing three N heteroatoms; wherein R^7, R^8, R^{11} and R^{12} are as previously defined herein or R^1 is a Het^4 group which is a C-linked 4- or 5-membered heterocyclic group containing one heteroatom selected from S, O or N; a Het^4 group which is a C-linked 6-membered heterocyclic group containing one, two or three heteroatoms selected from S or O; a Het^4 group which is a C-linked 6-membered heterocyclic group containing three nitrogen heteroatoms; a Het^4 group which is a C-linked 6-membered heterocyclic group containing one or two nitrogen heteroatoms which is substituted by one or more substitutents selected from C_1 to C_4 alkyl, C_1 to C_4 alkoxy, CO_2R^{11}, SO_2R^{12}, COR^{11}, NHR^{11} or $NHCOR^{12}$ and optionally including a further heteroatom selected from S, O or N wherein any of said heterocyclic groups Het^1, Het^2, Het^3 or Het^4 is saturated, partially unsaturated or aromatic as appropriate and wherein any of said heterocyclic groups is optionally substituted with one or more substituents selected from C_1 to C_4 alkyl, C_3 to C_4 alkenyl, C_1 to C_4 alkoxy, halo, CO_2R^{11}, SO_2R^{12}, COR^{11} or NHR^{11} wherein R^{11} is as defined hereinbefore and/or wherein any of said heterocyclic groups is benzo-fused; or R^1 is phenyl substituted by one or more substituents selected from CF_3, OCF_3, SO_2R^{12} or CO^2R^{12} wherein R^{12} is C_1 to C_4 alkyl which is optionally substituted by phenyl, C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy wherein said haloalkyl and haloalkoxy groups contain one or more halo atoms; R^2 is C_1 to C_6 alkyl; R^{13} is OR^3; R^3 is C_1 to C_6 alkyl optionally substituted with one or two substituents selected from C_3 to C_5 cycloalkyl, hydroxy, C_1 to C_4 alkoxy, benzyloxy, NR^5R^6, phenyl, furanyl, tetrahydrofuranyl or pyridinyl wherein said C_1 to C_6 alkyl and C_1 to C_4 alkoxy groups may optionally be terminated by a haloalkyl group such as CF_3; or R^3 is C_3 to C_6 cycloalkyl, 1-(C_1 to C_4 alkyl)piperidinyl, tetrahydrofuranyl or tetrahydropyranyl; R^4 is a piperazin-1-ylsulphonyl group having a substituent R^{10} at the 4-position of the piperazinyl group wherein said piperazinyl group is optionally substituted with one or two C_1 to C_4 alkyl groups and is optionally in the form of its 4-N-oxide; R^5 and R^6 are each independently selected from H and C_1 to C_4 alkyl optionally substituted with C_3 to C_5 cycloalkyl or C_1 to C_4 alkoxy, or, together with the nitrogen atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl group; and R^{10} is H; C_1 to C_4 alkyl optionally substituted with one or two substituents selected from hydroxy, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with C_1 to C_4 alkyl or C_1 to C_4 alkoxy; C_3 to C_6 alkenyl; Het^4; with the proviso that when R^1 is C_1 to C_3 alkyl substituted by phenyl then said phenyl group is not substituted by C_1 to C_4 alkoxy; CN; halo; CF_3; OCF_3; or C_1 to C_4 alkyl. More preferred of this group of compounds are those wherein R^1 is C_1 to C_6 alkyl wherein said alkyl may be branched or straight chain or R^1 is C_3 to C_6 cycloalkyl and wherein when R^1 is C_1 to C_3 alkyl said alkyl group is substituted by; and wherein when R^1 is C_4 to C_6 alkyl or C_3 to C_6 cycloalkyl said alkyl or cycloalkyl group is optionally substituted by; one or more substituents selected from: hydroxy; C_1 to C_2 alkoxy; C_3 to C_5 cycloalkyl; NR^7R^8,

NR^7COR^{11} or COR^{11} wherein R^7 and R^8 are each independently selected from H, C_1 to C_4 alkyl or CO_2R^9 wherein R^9 and R^{11} are as previously defined herein; a Het^1 group which is an N-linked 4-membered N-containing heterocyclic group; a Het^3 group which is a C-linked 6-membered heterocyclic group containing an O or S heteroatom optionally containing one or more heteroatoms selected from O, S or N or a Het^3 group which is a C-linked 6-membered heterocyclic group containing three N heteroatoms; or R^1 is a Het^4 group which is a C-linked 4-membered heterocyclic group containing one heteroatom selected from S, O or N or R^1 is a Het^4 group which is a C-linked 6-membered heterocyclic group containing one, two or three heteroatoms selected from S or O wherein any of said heterocyclic groups Het^1, Het^2, Het^3 or Het^4 is saturated, partially unsaturated or aromatic and is optionally substituted with one or more substituents selected from C_1 to C_4 alkyl, C_1 to C_4 alkoxy, $—CO_2R^{11}$, $—SO_2R^{12}$, $—COR^{11}$ or NHR^{11} wherein R^{11} and R^{12} are as defined hereinbefore and/or wherein any of said heterocyclic groups is benzo-fused; or R^1 is phenyl substituted by one or more substituents selected from: CF_3, $—OCF_3$, $—SO_2R^{12}$, $—COR^{11}$, $—CO_2R^{11}$ wherein R^{11} and R^{12} are as defined hereinbefore; R^2 is C_1 to C_6 alkyl; R^{13} is OR^3; R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl or t-butyl alkyl optionally substituted with one or two substituents selected from cyclopropyl, cyclobutyl, hydroxy, methoxy, ethoxy, benzyloxy, phenyl, benzyl, furan-3-yl, tetrahydrofuran-2-yl methyl, tetrahydrofuran-3-yl methyl, pyridin-2-yl, pyridin-3-yl or NR^5R^6 wherein R^5 and R^6 are each independently selected from H and C_1 to C_2 alkyl; R^4 is a piperazin-1-ylsulphonyl group having a substituent, R^{10} at the 4-position of the piperazinyl group wherein said piperazinyl group is optionally substituted with one or two C_1 to C_4 alkyl groups and is optionally in the form of its 4-N-oxide; and R^{10} is H, C_1 to C_3 alkyl optionally substituted with one or two substituents selected from hydroxy, NR^5R^6, $CONR^5R^6$ wherein R^5 and R^6 are each independently selected from H, C_1 to C_4 alkyl and C_3 alkenyl.

[0084] In formula (III), a further group of preferred compounds for use according to the present invention are those wherein: R^1 represents H, lower alkyl, Het, alkylHet, or alkylaryl (which latter four groups are all optionally substituted and/or terminated with one or more substituents selected from cyano, lower alkyl, OR^6, $C(O)OR^9$ or $NR^{12}R^{13}$); R^2 represents H, halo, lower alkyl, Het or aryl (which latter three groups are all optionally substituted and/or terminated with one or more substituents as defined hereinbefore, and preferably with $NR^{12}R^{13}$ or $SO_2NR^{14}R^{15}$); R^3 represents C_1-C_4 alkyl or C_3-C_4 cycloalkyl which are optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$); R^4 represents halo, cyano, nitro, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}OR^{11}$, $NR^{12}R^{13}$, $N[Y(O)R^{17}]_2$, $NR^{16}Y(O)R^{17}$, SOR^{18}, SO_2R^{19}, C(O)AZ, lower alkyl, alkynyl, Het or aryl, which latter three groups are all optionally substituted and/or terminated with one or more substituents as defined hereinbefore; and wherein Y, A, Z, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19} and Het are as herein before defined. More preferred in this further group are compounds in which R^1 represents optionally substituted lower alkyl, more preferably lower alkyl, lower alkoxy-terminated lower alkyl, $NR^{12}R^{13}$-terminated lower alkyl, or N-morpholino-terminated lower alkyl. Alternatively, R^1 may represent a 4-piperidinyl or a 3-azetidinyl group, optionally substituted at the nitrogen atom of the piperidinyl group with lower alkyl or $C(O)OR^9$. In such more preferred compounds in this further group R^2 represents $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, lower alkyl optionally interrupted by one or more of O, S or N, optionally substituted at N by lower alkyl or acyl, or optionally substituted aryl or Het. More preferably, when R^2 is interrupted lower alkyl, the interrupting atoms are one or more of O and lower alkylated-N and when R^2 is aryl, it is optionally substituted phenyl or pyridyl. Particularly preferred compounds of this further group are those in which R^2 represents $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, C_{1-4} alkyl optionally interrupted by O or N, optionally substituted at N by lower alkyl, optionally substituted phenyl, or optionally substituted pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrazin-2-yl, pyrazol-4-yl, oxadiazol-2-yl, furan-2-yl, furan-3-yl, tetrahydrofuran-2-yl and imidazo[1,2-a]pyridin-6-yl. In this more preferred group of further compounds R^3 may represent lower alkyl or cycloalkyl. Also, X is preferably O. Such further and more preferred compounds have R^4 representing halo, lower alkyl, lower alkynyl, optionally substituted Het, optionally substituted aryl, $C(O)R^8$, C(O)AZ, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ or $NR^{16}Y(O)R^{17}$. More preferred values for R^4 are $C(O)R^8$ (e.g. acetyl), halo (e.g. iodo), SO^2R^{19} (wherein R^{19} represents lower alkyl) and $C(O)NR^{10}R^{11}$ (e.g. where R^{10} and R^{11} independently represent H and lower alkyl and/or one of R^{10} and R^{11} is lower alkoxy) or NHB, wherein B represents H, SO_2CH_3 or C(O)Het. Further preferred still are compounds in which R^4 represents iodo, lower alkyl, lower alkynyl (which latter two groups are substituted and/or terminated by $C(O)OR^9$ (wherein R^9 represents H or C_{1-6} alkyl)), $N(H)Y(O)R^{17}$, $N[Y(O)R^{17}]_2$, optionally substituted Het or $NR^{12}R^{13}$ (wherein R^{12} and R^{13} together represent C_{3-5} alkylene interrupted by O or $N—S(O)_2$- (optionally substituted aryl)).

[0085] More preferred PDEV inhibitors for use with the invention, particularly with an alpha-2-delta ligand selected from gabapentin, pregabalin and (1α,3α,5α)(3-amino-methy-bicyclo[3.2.0]hept-3-yl) acetic acid, and pharmaceutically acceptable salts or solvates thereof, are selected from the group:

[0086] 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil);

[0087] (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (tadalafil, IC-351, Cialis®);

[0088] 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil);

[0089] 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

[0090] 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

[0091] 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-

5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine; and pharmaceutically acceptable salts and solvates thereof

[0092] A particularly preferred PDEV inhibitor, particularly with an alpha-2-delta ligand selected from gabapentin, pregabalin and (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0] hept-3-yl)-acetic acid, and pharmaceutically acceptable salts or solvates thereof, is 5-[2-ethoxy-5-(4-methyl-1-piperazinyl sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) and pharmaceutically acceptable salts or solvates thereof. Sildenafil citrate is a preferred salt.

[0093] As an alternative or further aspect of the present invention, there is provided a combination, particularly a synergistic combination, comprising gabapentin and a PDEV inhibitor selected from sildenafil, 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo [4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, vardenafil or tadalafil, or a pharmaceutically acceptable salt or solvate thereof. A particularly preferred combination comprises gabapentin and sildenafil or pharmaceutically acceptable salts or solvates thereof.

[0094] As an alternative or further aspect of the present invention, there is provided a combination, particularly a synergistic combination, comprising pregabalin and a PDEV inhibitor selected from sildenafil, 1-{6-ethoxy-5-[3-ethyl-6, 7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d] pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, vardenafil or tadalafil. A particularly preferred combination comprises pregabalin and sildenafil.

[0095] As a yet further alternative or preferred aspect of the present invention, there is provided a combination, particularly a synergistic combination, comprising [(1R,5R, 6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid or a pharmaceutically acceptable salt or solvate thereof, and a PDEV inhibitor. Suitably, there is provided a combination comprising [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid or a pharmaceutically acceptable salt or solvate thereof, and a PDEV inhibitor selected from sildenafil, 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methozyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsufonyl}-4-ethylpiperazine, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one, vardenafil or tadalafil or a pharmaceutically acceptable salt or solvate thereof, preferably sildenafil or a pharmaceutically acceptable salt or solvate thereof.

[0096] Suitably, there is provided a combination comprising (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid or a pharmaceutically acceptable salt or solvate thereof, and a PDEV inhibitor selected from sildenafil, 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethy)-7-oxo-2H-pyraxolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one, vardenafil or tadalafil or a pharmaceutically acceptable salt or solvate thereof, preferably sildenafil or a pharmaceutically acceptable salt or solvate thereof.

[0097] As a yet further preferred aspect of the present invention, the combination is selected from:

[0098] gabapentin and sildenafil;

[0099] gabapentin and vardenafil;

[0100] gabapentin and tadalafil;

[0101] gabapentin and 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4, 3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine;

[0102] gabapentin and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

[0103] pregabalin and sildenafil;

[0104] pregabalin and vardenafil;

[0105] pregabalin and tadalafil;

[0106] pregabalin and 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine;

[0107] pregabalin and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

[0108] [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, and sildenafil;

[0109] [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, and vardenafil;

[0110] [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, and tadalafil;

[0111] [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, and 1-{6-ethoxy-5-[3-ethyl-6, 7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyraxolo [4,3-d]pyrimidin-5-yl]-3-pyridyl sulfonyl}-4-ethylpiperazine; and

[0112] [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

[0113] (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0] hept-3-yl)-acetic acid, and sildenafil;

[0114] (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0] hept-3-yl)-acetic acid, and vardenafil;

[0115] (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0] hept-3-yl)-acetic acid, and tadalafil;

[0116] (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0] hept-3-yl)-acetic acid, and 1-{6-ethoxy-5-[3-ethyl-6, 7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyraxolo [4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine; and

[0117] (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0] hept-3-yl)-acetic acid, and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

[0118] (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, and sildenafil;

[0119] (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, and vardenafil;

[0120] (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, and tadalafil;

[0121] (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, and 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine,

[0122] (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

[0123] or pharmaceutically acceptable salts or solvates of any thereof.

[0124] The combination of the present invention in a single dosage form is suitable for administration to any mammalian subject, preferably human. Administration may be once (o.d.), twice (b.i.d.) or three times (t.i.d.) daily, suitably b.i.d. or t.i.d., more suitably b.i.d, most suitably o.d. Thus, as a further aspect of the present invention, there is provided a method of curative, prophylactic or palliative treatment of pain in a mammalian subject comprising once, twice or thrice, suitably twice or thrice, more suitably twice, most suitably once daily administration of an effective, particularly synergistic, combination of an alpha-2-delta ligand and a PDEV inhibitor.

[0125] Determining a synergistic interaction between one or more components, the optimum range for the effect and absolute dose ranges of each component for the effect may be definitively measured by administration of the components over different w/w ratio ranges and doses to patients in need of treatment. For humans, the complexity and cost of carrying out clinical studies on patients renders impractical the use of this form of testing as a primary model for synergy. However, the observation of synergy in one species can be predictive of the effect in other species and animal models exist, as described herein, to measure a synergistic effect and the results of such studies can also be used to predict effective dose and plasma concentration ratio ranges and the absolute doses and plasma concentrations required in other species by the application of pharmacokinetic/pharmacodynamic methods. Established correlations between animal models and effects seen in man suggest that synergy in animals is best-demonstrated using static and dynamic allodynia measurements in rodents that have undergone surgical (e.g. chronic constriction injury) or chemical (e.g. streptozocin) procedures to induce the allodynia. Because of plateau effects in such models, their value is best assessed in terms of synergistic actions that in neuropathic pain patients would translate to dose-sparing advantages. Other models in which existing agents used for the treatment of neuropathic pain give only a partial response are more suited to predict the potential of combinations acting synergistically to produce increased maximal efficacy at maximally tolerated doses of the two components.

[0126] Thus, as a further aspect of the present invention, there is provided a synergistic combination for human administration comprising an alpha-2-delta ligand and a PDEV inhibitor, or pharmaceutically acceptable salts or solvates thereof, in a w/w combination range which corresponds to the absolute ranges observed in a nonhuman animal model, preferably a rat model, primarily used to identify a synergistic interaction. Suitably, the ratio range in humans corresponds to a non-human range selected from between 1:50 to 50:1 parts by weight, 1:50 to 20:1, 1:50 to 10:1, 1:50 to 1:1, 1:20 to 50:1, 1:20 to 20:1, 1:20 to 10:1, 1:20 to 1:1, 1:10 to 50:1, 1:10 to 20:1, 1:10 to 10:1, 1:10 to 1:1, 1:1 to 50:1, 1.1 to 20:1 and 1:1 to 10:1. More suitably, the human range corresponds to a synergistic non-human range of 1:10 to 20:1 parts by weight. Preferably, the human range corresponds to a non-human range of the order of 1:1 to 10:1 parts by weight. For gabapentin and sildenafil, the human range corresponds to a synergistic dose range in a non-human, preferably rat, model of the order of 1:1 to 10:1 parts by weight.

[0127] For humans, several experimental pain models may be used in man to demonstrate that agents with proven synergy in animals also have effects in man compatible with that synergy. Examples of human models that may be fit for this purpose include the heat/capsaicin model (Petersen, K. L. & Rowbotham, M. C. (1999) NeuroReport 10, 1511-1516), the i.d capsaicin model (Andersen, O. L., Felsby, S., Nicolaisen, L., Bjerring, P., Jsesn, T. S. & Arendt-Nielsen, L. (1996) Pain 66, 51-62), including the use of repeated capsaicin trauma (Witting, N., Svesson, P., Arendt-Nielsen, L. &Jensen, T. S. (2000) Somatosensory Motor Res. 17, 5-12), and summation or wind-up responses (Curatolo, M. et al. (2000) Anesthesiology 93, 1517-1530). With these models, subjective assessment of pain intensity or areas of hyperalgesia may be used as endpoints, or more objective endpoints, reliant on electrophysiological or imaging technologies (such as functional magnetic resonance imaging) may be employed (Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C. & Buchel, C. (2002) Brain 125, 1326-1336). All such models require evidence of objective validation before it can be concluded that they provide evidence in man of supporting the synergistic actions of a combination that have been observed in animal studies.

[0128] For the present invention in humans, a suitable alpha-2-delta ligand:PDEV inhibitor ratio range is selected from between 1:50 to 50:1 parts by weight, 1:50 to 20:1, 1:50 to 10:1, 1:50 to 1:1, 1:20 to 50:1, 1:20 to 20:1, 1:20 to 10:1, 1:20 to 1:1, 1:10 to 50:1, 1:10 to 20:1, 1:10 to 10:1, 1:10 to 1:1, 1:1 to 50:1, 1.1 to 20:1 and 1:1 to 10:1, more suitably 1:10 to 20:1, preferably, 1:1 to 10:1. For a combination of gabapentin and sildenafil, the invention provides a suitable dose in the ratio range of 1:10 to 10:1 w/w, more suitably 1:5 to 5:1 respectively.

[0129] Optimal doses of each component for synergy can be determined according to published procedures in animal models. However, in man (even in experimental models of pain) the cost can be very high for studies to determine the entire exposure-response relationship at all therapeutically relevant doses of each component of a combination. It may be necessary, at least initially, to estimate whether effects can be observed that are consistent with synergy at doses that have been extrapolated from those that give optimal synergy in animals. In scaling the doses from animals to man, factors such as relative body weight/body surface area, relative absorption, distribution, metabolism and excretion of each component and relative plasma protein binding need to be considered and, for these reasons, the optimal dose ratio predicted for man (and also for patients) is unlikely to be the

same as the dose ratio shown to be optimal in animals. However, the relationship between the two can be understood and calculated by one skilled in the art of animal and human pharmacokinetics. Important in establishing the bridge between animal and human effects are the plasma concentrations obtained for each component used in the animal studies, as these are related to the plasma concentration of each component that would be expected to provide efficacy in man. Pharmacokinetic/pharmacodynamic modeling (including methods such as isobolograms, interaction index and response surface modelling) and simulations may help to predict synergistic dose ratios in man, particularly where either or both of these components has already been studied in man.

[0130] It is important to ascertain whether any concluded synergy observed in animals or man is due solely to pharmacokinetic interactions. For example, inhibition of the metabolism of one compound by another might give a false impression of pharmacodynamic synergy. In animal studies with gabapentin and sildenafil, repeated blood samples have been taken and it has been shown that, in accordance with the known pharmacokinetic properties of the agents, there is no evidence of any pharmacokinetic interaction when the compounds are administered at the doses that induced synergistic pain interactions. This proves that the synergy with respect to pain is pharmacodynamic, occurring subsequent to each of these agents interacting with their respective receptor and/or enzyme targets.

[0131] Thus, according to a further aspect of the present invention, there is provided a synergistic combination for administration to humans comprising an alpha-2-delta ligand and a PDEV inhibitor or pharmaceutically acceptable salts or solvates thereof, where the dose range of each component corresponds to the absolute synergistic ranges observed in a non-human animal model, preferably the rat model, primarily used to identify a synergistic interaction. Suitably, the dose range of alpha-2-delta ligand in human corresponds to a dose range of 1-20 mg/kg, more suitably 1-10 mg/kg, in the rat and the corresponding dose range for a PDEV inhibitor is 0.1-10 mg/kg, more suitably 0.1-1 mg/kg. For gabapentin and sildenafil, the dose range in the human suitably corresponds to a synergistic range of 1-10 mg/kg gabapentin and 0.1-1 mg/kg sildenafil in the rat.

[0132] Suitably, the dose of alpha-2-delta ligand for use in a human is in a range selected from 1-1200 mg, 1-500 mg, 1-100 mg, 1-50 mg, 1-25 mg, 500-1200 mg, 100-1200 mg, 100-500 mg, 50-1200 mg, 50-500 mg, or 50-100 mg, suitably 50-100 mg, b.i.d. or t.i.d., suitably t.i.d., and the dose of PDEV inhibitor is in a range selected from 1-200 mg, 1-100 mg, 1-50 mg, 1-25 mg, 10-100 mg, 10-50 mg or 10-25 mg, suitably 10-100 mg, b.i.d or t.i.d, suitably t.i.d. For gabapentin and sildenafil, the suitable dose ranges are 50-600 mg: 10-100 mg t.i.d.

[0133] It will be apparent to the skilled reader that the plasma concentration ranges of the alpha-2-delta ligand and PDEV inhibitor combinations of the present invention required to provide a therapeutic effect depend on the species to be treated, and components used. For example, for gabapentin and sildenafil in the rat the Cmax values of gabapentin range from 0.520 μg/ml to 10.5 μg/ml and the Cmax values of sildenafil range from 0.02 μg/ml to 2.1 μg/ml.

[0134] It is possible, using standard PK/PD and allometric methods, to extrapolate the plasma concentration values observed in an animal model to predict the values in a different species, particularly human. Thus, as a further aspect of the present invention, there is provided a synergistic combination for administration to humans comprising an alpha-2-delta ligand and a PDEV inhibitor, where the plasma concentration range of each component corresponds to the absolute ranges observed in a non-human animal model, preferably the rat model, primarily used to identify a synergistic interaction. Suitably, the plasma concentration range in the human corresponds to a range of 0.05 μg/ml to 10.5 μg/ml for an alpha-2-delta ligand and 0.005 μg/ml to 2.1 μg/ml for a PDEV inhibitor in the rat model. For gabapentin and sildenafil, the plasma concentration range in the human corresponds to a range of 0.05 μg/ml to 10.5 μg/ml for gabapentin and 0.005 μg/ml to 2.1 μg/ml for sildenafil in the rat model. Since protein-binding properties are similar in rat and human plasma for both compounds, the plasma concentration ranges above are relevant to human.

[0135] Thus, an alternative aspect, the present invention provides a synergistic combination comprising an alpha-2-delta ligand and a PDEV inhibitor, or pharmaceutically acceptable salts or solvates thereof, where the plasma concentration range for the components comprises Cmax values of up to 20 μg/ml for the alpha-2-delta ligand and up to 4 μg/ml for a PDEV inhibitor, more suitably 0.5 μg/ml to 10 μg/ml and 0.02 μg/ml to 2.1 μg/ml, preferably 0.05 μg/ml to 20 μg/ml and 0.005 μg/ml to 4 μg/ml respectively.

[0136] Particularly preferred combinations of the invention include those in which each variable of the combination is selected from the suitable parameters for each variable. Even more preferable combinations of the invention include those where each variable of the combination is selected from the more suitable, most suitable, preferred or more preferred parameters for each variable.

BRIEF DESCRIPTION OF THE DRAWINGS

[0137] **FIG. 1**. Effect of (a) gabapentin and (b) sildenafil on the maintenance of CCI-induced static allodynia. Baseline (BL) paw withdrawal thresholds (PWT) to von Frey hairs were determined in CCI animals before drug administration. PWT were re-examined up to 4 h post drug. Results are expressed as median force (g) required to induce paw withdrawal (vertical bars represent 1st and 3rd quartiles). *P<0.05**P<0.01***P<0.005 significantly different (Mann Whitney U test) from vehicle treated group at each time point.

[0138] **FIG. 2**. Effect of (a) gabapentin and (b) sildenafil on the maintenance of CCI-induced dynamic allodynia. Baseline (BL) paw withdrawal latencies (PWL) to cotton bud stimulus were determined for right hind paw before drug administration. PWL's were re-examined for up to 4 hours. Results are expressed as mean PWL (s) vertical bars represent ±SEM*P<0.05, **P<0.01, Significantly different (ANOVA followed by a Dunnett's t-test) from vehicle treated group at each time point.

[0139] **FIG. 3**. Effect of fixed dose ratios of gabapentin and sildenafil on the maintenance of CCI-induced static allodynia. All data is expressed at the 2 h time point post drug administration. Dose-response data for gabapentin and sildenafil alone were taken from **FIG. 1**. Fixed dose ratios of

(a) 1:10 (b) 1:1 (c) 10:1 (d) 20:1 gabapentin and sildenafil combinations. Results are expressed as median force (g) required to induce paw withdrawal (vertical bars represent 1st and 3rd quartiles).

[0140] **FIG. 4**. Effect of fixed dose ratios of gabapentin and sildenafil on the maintenance of CCI-induced dynamic allodynia. All data is expressed at the 2 h time point post drug administration. Dose-response data for gabapentin and sildenafil alone were taken from **FIG. 2**. Fixed dose ratios of (a) 1:10 (b) 1:1 (c) 10:1 (d) 20:1 gabapentin and sildenafil combinations. Results are expressed as mean PWL (s) vertical bars represent ±SEM*P<0.05, **P<0.01, Significantly different (ANOVA followed by a Dunnett's t-test) from vehicle treated group at each time point.

DETAILED DESCRIPTION OF THE INVENTION

[0141] The compounds of the present combination invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, which may contain isotopic substitutions (e.g. D2O, d6-acetone, d6-DMSO), are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

[0142] Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof. Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the invention or a suitable salt or derivative thereof.

[0143] A number of alpha-2-delta ligands of the present invention are amino acids. Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate non-toxic inorganic or organic acids or bases. Suitable acid addition salts are the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate, camsylate, citrate, edisylate, esylate, fumarate, gluceptate, gluconate, glucuronate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, hydrogen phosphate, isethionate, D- and L-lactate, malate, maleate, malonate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, palmoate, phosphate, saccharate, stearate, succinate sulphate, D- and L-tartrate, and tosylate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc, choline, diolamine, olamine, arginine, glycine, tromethamine, benzathine, lysine, meglumine and diethylamine salts. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The compounds of the invention may also be formed as a zwitterion. Furthermore, since a number of the PDEV inhibitors of the present invention are amines and a number of the alpha-2-delta ligands have an acid functionality, a further aspect of the present invention comprises a salt form containing the 2 components, particularly in a 1:1 combination. A suitable combination salt form is the salt formed by a 1:1 combination of gabapentin and sildenafil.

[0144] A suitable salt for amino acid compounds of the present invention is the hydrochloride salt. For a review on suitable salts see Stahl and Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-VCH, Weinheim, Germany (2002).

[0145] Also within the scope of the invention are clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in non-stoichiometric amounts. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

[0146] Hereinafter all references to compounds of the invention include references to salts thereof and to solvates and clathrates of compounds of the invention and salts thereof.

[0147] Also included within the present scope of the compounds of the invention are polymorphs thereof.

[0148] Prodrugs of the above compounds of the invention are included in the scope of the instant invention. The chemically modified drug, or prodrug, should have a different pharmacokinetic profile to the parent, enabling easier absorption across the mucosal epithelium, better salt formulation and/or solubility, improved systemic stability (for an increase in plasma half-life, for example). These chemical modifications may be

[0149] (1) Ester or amide derivatives which may be cleaved by, for example, esterases or lipases. For ester derivatives, the ester is derived from the carboxylic acid moiety of the drug molecule by known means. For amide derivatives, the amide may be derived from the carboxylic acid moiety or the amine moiety of the drug molecule by known means.

[0150] (2) Peptides which may be recognized by specific or nonspecific proteinases. A peptide may be coupled to the drug molecule via amide bond formation with the amine or carboxylic acid moiety of the drug molecule by known means.

[0151] (3) Derivatives that accumulate at a site of action through membrane selection of a prodrug form or modified prodrug form.

[0152] (4) Any combination of 1 to 3.

[0153] Aminoacyl-glycolic and -lactic esters are known as prodrugs of amino acids (Wermuth C. G., *Chemistry and Industry*, 1980:433-435). The carbonyl group of the amino acids can be esterified by known means. Prodrugs and soft drugs are known in the art (Palomino E., *Drugs of the Future*, 1990;15(4):361-368). The last two citations are hereby incorporated by reference.

[0154] The combination of the present invention is useful for the general treatment of pain, particularly neuropathic pain. Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is exclusively activated by noxious stimuli via peripheral transducing mechanisms (Millan 1999 Prog. Neurobio. 57:1-164 for an integrative Review). These sensory fibres are known as nociceptors and are characterised by small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised

projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred after complex processing in the dorsal horn, either directly or via brain stem relay nuclei to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

[0155] Intense acute pain and chronic pain may involve the same pathways driven by pathophysiological processes and as such cease to provide a protective mechanism and instead contribute to debilitating symptoms associated with a wide range of disease states. Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered. There is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. This leads to hypersensitivity at the site of damage and in nearby normal tissue. In acute pain these mechanisms can be useful and allow for the repair processes to take place and the hypersensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury. This injury often leads to maladaptation of the afferent fibres (Woolf & Salter 2000 Science 288: 1765-1768). Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. There are a number of typical pain subtypes: 1) spontaneous pain which may be dull, burning, or stabbing; 2) pain responses to noxious stimuli are exaggerated (hyperalgesia); 3) pain is produced by normally innocuous stimuli (allodynia) (Meyer et al., 1994 Textbook of Pain 13-44). Although patients with back pain, arthritis pain, CNS trauma, or neuropathic pain may have similar symptoms, the underlying mechanisms are different and, therefore, may require different treatment strategies. Therefore pain can be divided into a number of different areas because of differing pathophysiology, these include nociceptive, inflammatory, neuropathic pain etc. It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. Back pain, Cancer pain can have nociceptive inflammatory and neuropathic components.

[0156] Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and sensitise the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994 Textbook of Pain 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmitted rapidly and are responsible for the sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey the dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to pain from strains/sprains, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, burns, myocardial infarction, acute pancreatitis, and renal colic. Also cancer related acute pain syndromes commonly due to therapeutic interactions such as chemotherapy toxicity, immunotherapy, hormonal therapy and radiotherapy. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to, cancer pain which may be tumour related pain, (e.g. bone pain, headache and facial pain, viscera pain) or associated with cancer therapy (e.g. postchemotherapy syndromes, chronic postsurgical pain syndromes, post radiation syndromes), back pain which may be due to herniated or ruptured intervertebral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament

[0157] Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (IASP definition). Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include but are not limited to, diabetic neuropathy, post herpetic neuralgia, back pain, cancer neuropathy, chemotherapy-induced neuropathy, HIV neuropathy, Phantom limb pain, Carpal Tunnel Syndrome, chronic alcoholism, hypothyroidism, trigeminal neuralgia, uremia, trauma-induced neuropathy, or vitamin deficiencies. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patients quality of life (Woolf and Mannion 1999 Lancet 353: 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd 1999 Pain Supp. 6: S141-S147; Woolf and Mannion 1999 Lancet 353: 1959-1964). They include spontaneous pain, which can be continuous, or paroxysmal and abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

[0158] The inflammatory process is a complex series of biochemical and cellular events activated in response to tissue injury or the presence of foreign substances, which result in swelling and pain (Levine and Taiwo 1994: Textbook of Pain 45-56). Arthritic pain makes up the majority of the inflammatory pain population. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis (RA) is a common cause of disability. The exact aetiology of RA is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson 1994 Textbook of Pain 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder 2002 Ann Pharmacother. 36: 679-686; McCarthy et al., 1994 Textbook of Pain 387-395). Most patients with OA seek medical attention because of pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Other types of inflammatory pain include but are not limited to inflammatory bowel diseases (IBD),

[0159] Other types of pain include but are not limited to;

[0160] Musculo-skeletal disorders including but not limited to myalgia, fibromyalgia, spondylitis, seronegative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, Glycogenolysis, polymyositis, pyomyositis.

[0161] Central pain or 'thalamic pain' as defined by pain caused by lesion or dysfunction of the nervous system including but not limited to central post-stroke pain, multiple sclerosis, spinal cord injury, Parkinson's disease and epilepsy.

[0162] Heart and vascular pain including but not limited to angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, sclerodoma, skeletal muscle ischemia.

[0163] Visceral pain, and gastrointestinal disorders. The viscera encompasses the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera may be neuropathic, nociceptive as well as inflammatory and can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the inflammatory bowel diseases (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including—for FBD, gastro-esophageal reflux, dyspepsia, the irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and—for IBD, Crohn's disease, ileitis, and ulcerative colitis, which all regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis.

[0164] Head pain including but not limited to migraine, migraine with aura, migraine without aura, cluster headache, tension-type headache.

[0165] Orofacial pain including but not limited to dental pain, temporomandibular myofascial pain.

[0166] Thus, as a yet further aspect, there is provided the simultaneous, sequential or separate use of an alpha-2-delta ligand, excluding compounds of formula (i)-(xxv) of PCT/IB02/01146 and pregabalin or gabapentin, where the exclusion of pregabalin or gabapentin is limited to use in the treatment of neuropathy, and a PDEV inhibitor in the manufacture of a medicament for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain. As a preferred feature, the use suitably comprises any one of the combinations mentioned herein above.

[0167] As an alternative aspect, there is provided a method for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain, comprising simultaneous, sequential or separate administration of a therapeutically effective amount of an alpha-2-delta ligand, excluding pregabalin or gabapentin, where the exclusion of pregabalin or gabapentin is limited to use in the treatment of neuropathy, and a PDEV inhibitor to a mammal in need of said treatment. As an alternative aspect, the exclusion may the include compounds of formula (i)-(xxv) of PCT/IB02/01146. As a preferred feature, the method suitably comprises any one of the combinations mentioned herein above.

[0168] As an alternative aspect, there is provided the simultaneous, sequential or separate use of a synergistic combination of an alpha-2-delta ligand and a PDEV inhibitor in the manufacture of a medicament for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain. As a preferred feature, the use suitably comprises any one of the combinations mentioned herein above.

[0169] As a further alternative aspect, there is provided a method for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain, comprising simultaneous, sequential or separate administration of a therapeutically synergistic amount of an alpha-2-delta ligand and a PDEV inhibitor to a mammal in need of said treatment. As a preferred feature, the method suitably comprises any one of the combinations mentioned herein above.

[0170] The biological activity of the alpha-2-delta ligands of the invention may be measured in a radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue (Gee N. S., Brown J. P., Dissanayake V. U. K., Offord J., Thurlow R., Woodruff G. N., *J. Biol. Chem.*, 1996;271 :5879-5776). Results may be expressed in terms of μM or nM $\alpha 2\delta$ binding affinity.

[0171] In vitro inhibitory activities of the PDEV inhibitors of the present invention against cyclic guanosine monophosphate (cGMP) may be determined by measurement of their IC_{50} values, according to the details described in WO01/27113. Functional activity can be assessed as described by S A Ballard et al (Brit. J. Pharmacology, 1996, 118 (suppl.), abstract 153P).

[0172] The elements of the combination of the instant invention may be administered separately, simultaneously or sequentially. As a further aspect of the present invention, there is provided a package comprising a synergistic combination of an alpha-2-delta ligand and a PDEV inhibitor and a suitable container.

[0173] The combination of the present invention may also optionally be administered with one or more other pharmacologically active agents. Suitable optional agents include:

[0174] (i) opioid analgesics, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, buprenorphine, butorphanol, nalbuphine and pentazocine;

[0175] (ii) Opioid antagonists, e.g. naloxone, naltrexone

[0176] (iii) nonsteroidal antiinflammatory drugs (NSAIDs), e.g. aspirin, diclofenac, difluinsal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and their pharmaceutically acceptable salts or solvates;

[0177] (iv) barbiturate sedatives, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal, thiopental and their pharmaceutically acceptable salts or solvates;

[0178] (v) benzodiazepines having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam and their pharmaceutically acceptable salts or solvates,

[0179] (vi) H_1 antagonists having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine, chlorcyclizine and their pharmaceutically acceptable salts or solvates;

[0180] (vii) miscellaneous sedatives such as glutethimide, meprobamate, methaqualone, dichloralphenazone and their pharmaceutically acceptable salts or solvates;

[0181] (viii) skeletal muscle relaxants, e.g. baclofen, tolperisone, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, orphrenadine and their pharmaceutically acceptable salts or solvates,

[0182] (ix) NMDA receptor antagonists, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid and their pharmaceutically acceptable salts or solvates;

[0183] (x) alpha-adrenergic active compounds, e.g. doxazosin, tamsulosin, clonidine and 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

[0184] (xi) tricyclic antidepressants, e.g. desipramine, imipramine, amytriptiline and nortriptiline;

[0185] (xii) anticonvulsants, e.g. carbamazepine, valproate, lamotrigine;

[0186] (xiii) serotonin reuptake inhibitors, e.g. fluoxetine, paroxetine, citalopram and sertraline;

[0187] (xiv) mixed serotonin-noradrenaline reuptake inhibitors, e.g. milnacipran, venlafaxine and duloxetine;

[0188] (xv) noradrenaline reuptake inhibitors, e.g. reboxetine;

[0189] (xvi) Tachykinin (NK) antagonists, particularly Nk-3, NK-2 and NK-1 antagonists e.g., (αR, 9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4] diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl] methylamino]-2-phenyl-piperidine (2S,3S)

[0190] (xvii) Muscarinic antagonists, e.g oxybutin, tolterodine, propiverine, tropsium chloride and darifenacin;

[0191] (xviii) COX-2 inhibitors, e.g. celecoxib, rofecoxib and valdecoxib;

[0192] (xix) Non-selective COX inhibitors (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);

[0193] (xx) coal-tar analgesics, in particular, paracetamol;

[0194] (xxi) neuroleptics, such as droperidol;

[0195] (xxii) Vanilloid receptor agonists, e.g. resinferatoxin;

[0196] (xxiii) Beta-adrenergic compounds such as propranolol;

[0197] (xxiv) Local anaesthetics, such as mexiletine, lidocaine;

[0198] (xxv) Corticosteriods, such as dexamethasone

[0199] (xxvi) serotonin receptor agonists and antagonists;

[0200] (xxvii) cholinergic (nicotinic) analgesics; and

[0201] (xxviii) miscellaneous agents such as Tramadol®.

[0202] Thus, the present invention extends to a combination product comprising an alpha-2-delta ligand, a PDEV inhibitor, and one or more other therapeutic agents, such as one of those listed above, for simultaneous, separate or sequential use in the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain.

[0203] The combination of the invention can be administered alone but one or both elements will generally be administered in an admixture with suitable pharmaceutical excipient(s), diluent(s) or carrier(s) selected with regard to the intended route of administration and standard pharmaceutical practice. If appropriate, auxiliaries can be added. Auxiliaries are preservatives, anti-oxidants, flavours or colourants. The compounds of the invention may be of immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release type.

[0204] The elements of the combination of the present invention can be administered, for example but not limited to, the following route: orally, buccally or sublingually in the form of tablets, capsules, multi-and nano-particulates, gels, films (incl. muco-adhesive), powder, ovules, elixirs, lozenges (incl. liquid-filled), chews, solutions, suspensions and sprays. The compounds of the invention may also be administered as osmotic dosage form, or in the form of a high energy dispersion or as coated particles or fast-dissolving, fast -disintegrating dosage form as described in Ashley Publications, 2001 by Liang and Chen. The compounds of the invention may be administered as crystalline or amorphous products, freeze dried or spray dried. Suitable formulations of the compounds of the invention may be in hydrophilic or hydrophobic matrix, ion-exchange resin complex, coated or uncoated form and other types as described in U.S. Pat. No. 6,106,864 as desired. Such pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), mannitol, disintegrants such as sodium starch glycolate, crosscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), triglycerides, hydroxypropylcellulose (HPC), bentonite sucrose, sorbitol, gelatin and acacia. Additionally, lubricating agents may be added to solid compositions such as magnesium stearate, stearic acid, glyceryl behenate, PEG and talc or wetting agents, such as sodium lauryl sulphate. Additionally, polymers such as carbohydrates, phospoholipids and proteins may be included.

[0205] Fast dispersing or dissolving dosage fromulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol or xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used, i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

[0206] The solid dosage form, such as tablets are manufactured by a standard process, for example, direct compression or a wet, dry or melt granulation, melt congealing and extrusion process. The tablet cores which may be mono or multi-layer may be coated with appropriate overcoats known in the art.

[0207] Solid compositions of a similar type may also be employed as fillers in capsules such as gelatin, starch or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. Liquid compositions may be employed as fillers in soft or hard capsules such as gelatin capsule. For aqueous and oily suspensions, solutions, syrups and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol, methylcellulose, alginic acid or sodium alginate, glycerin, oils, hydrocolloid agents and combinations thereof. Moreover, formulations containing these compounds and excipients may be presented as a dry product for constitution with water or other suitable vehicles before use.

[0208] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0209] The elements of the combination of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, intraduodenally, or intraperitoneally, intraarterially, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intraspinally or subcutaneously, or they may be administered by infusion, needle-free injectors or implant injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution, suspension or emulsion (or system so that can include micelles) which may contain other substances known in the art, for example, enough salts or carbohydrates such as glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. For some forms of parenteral administration they may be used in the form of a sterile non-aqueous system such as fixed oils, including mono- or diglycerides, and fatty acids, including oleic acid. The preparation of suitable parenteral formulations under sterile conditions for example lyophilisation is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (e.g. sterile, pyrogen-free water) before use.

[0210] Also, the elements of the combination of the present invention can be administered intranasally or by inhalation. They are conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist) or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubron (trade mark) or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol (optionally, aqueous ethanol) or a suitable agent for dispersing, solubilising or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

[0211] Prior to use in a dry powder formulation or suspension formulation for inhalation the elements of the combination of the invention will be micronised to a size suitable for delivery by inhalation (typically considered as less than 5 microns). Micronisation could be achieved by a range of methods, for example spiral jet milling, fluid bed jet milling, use of supercritical fluid crystallisation or by spray drying.

[0212] A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1 μg to 10 mg of the compound of the invention per actuation and the actuation volume may vary from 1 to 100 μl. A typical formulation may comprise a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents may be used in place of propylene glycol, for example glycerol or polyethylene glycol.

[0213] Alternatively, the elements of the combination of the invention may be administered topically to the skin, mucosa, dermally or transdermally, for example, in the form of a gel, hydrogel, lotion, solution, cream, ointment, dusting

powder, dressing, foam, film, skin patch, wafers, implant, sponges, fibres, bandage, microemulsions and combinations thereof. For such applications, the compounds of the invention can be suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, water, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, alcohols such as ethanol. Alternatively, penetration enhancers may be used. The following may also be used polymers, carbohydrates, proteins, phospolipids in the form of nanoparticles (such as niosomes or liposomes) or suspended or dissolved. In addition, they may be delivered using iontophoresis, electroporation, phonophoresis and sonophoresis.

[0214] Alternatively, the elements of the combination of the invention can be administered rectally, for example in the form of a suppository or pessary. They may also be administered by vaginal route. For example, these compositions may be prepared by mixing the drug with a suitable non-irritant excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the cavity to release the drug.

[0215] The elements of the combination of the invention may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline. A polymer may be added such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer (e.g. hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), or a heteropolysaccharide polymer (e.g. gelan gum). Alternatively, they may be formulated in an ointment such as petrolatum or mineral oil, incorporated into bio-degradable (e.g. absorbable gel sponges, collagen) or non-biodegradable (e.g. silicone) implants, wafers, drops, lenses or delivered via particulate or vesicular systems such as niosomes or liposomes. Formulations may be optionally combined with a preservative, such as benzalkonium chloride. In addition, they may be delivered using iontophoresis. They may also be administered in the ear, using for example but not limited to the drops.

[0216] The elements of the combination of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, taste-masking, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

[0217] The term 'administered' includes delivery by viral or non-viral techniques. Viral delivery mechanisms include but are not limited to adenoviral vectors, adeno-associated viral (AAV) vectors, herpes viral vectors, retroviral vectors, lentiviral vectors, and baculoviral vectors. Non-viral delivery mechanisms include lipid mediated transfection, liposomes, immunoliposomes, lipofectin, cationic facial amphiphiles (CFAs) and combinations thereof. The routes for such delivery mechanisms include but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

[0218] Thus, as a further aspect of the present invention, there is provided a pharmaceutical composition comprising a combination comprising an alpha-2-delta ligand, excluding gabapentin, pregabalin, a PDEV inhibitor and a suitable excipient, diluent or carrier. Alternatively, the exclusion may include the compounds of formula (i)-(xxv) of PCT/IB02/01146. Suitably, the composition is suitable for use in the treatment of pain, particularly neuropathic pain.

[0219] As an alternative aspect of the present invention, there is provided a pharmaceutical composition comprising a synergistic combination comprising an alpha-2-delta ligand, a PDEV inhibitor and a suitable excipient, diluent or carrier. Suitably, the composition is suitable for use in the treatment of pain, particularly neuropathic pain.

[0220] For non-human animal administration the term 'pharmaceutical' as used herein may be replaced by 'veterinary'.

[0221] The element of the pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The quantity of active component in a unit dose preparation may be varied or adjusted according to the particular application and the potency of the active components. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compounds. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0222] For veterinary use, a combination according o the present invention or veterinarily acceptable salts or solvates thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

BIOLOGY EXAMPLES

Methods

Animals

[0223] Male Sprague Dawley rats (200-250 g), obtained from Charles River, (Margate, Kent, U.K.) were housed in groups of 6. All animals were kept under a 12 h light/dark cycle (lights on at 07 h 00 min) with food and water ad libitum. All experiments were carried out by an observer unaware of drug treatments.

CCI Surgery in the Rat

[0224] Animals were anaesthetised with isoflurane. The sciatic nerve was ligated as previously described by Bennett and Xie, 1988. Animals were placed on a homeothermic blanket for the duration of the procedure. After surgical preparation the common sciatic nerve was exposed at the middle of the thigh by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7 mm of nerve was freed of adhering tissue and 4 ligatures (4-0 silk) were tied loosely around it with about 1 mm spacing. The incision was closed in layers and the wound treated with topical antibiotics.

Effect of Combinations on the Maintenance of CCI-Induced Static and Dynamic Allodynia

[0225] Dose-responses to gabapentin and sildenafil were first performed alone in the CCI model. Combinations were examined following a fixed ratio design. A dose-response to each fixed dose ratio of the combination was performed. On each test day, baseline paw withdrawal thresholds (PWT) to von Frey hairs and paw withdrawal latencies (PWL) to a cotton bud stimulus were determined prior to drug treatment. Gabapentin was administered p.o. directly followed by s.c. administration of sildenafil and PWT and PWL re-examined for up to 5 h. The data are expressed at the 2 h time point for both the static and dynamic data as this timepoint represent the peak antiallodynic effects.

Evaluation of Allodynia

[0226] Static allodynia was measured using Semmes-Weinstein von Frey hairs (Stoelting, Ill., U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Static allodynia was tested by touching the plantar surface of the animals right hind paw with von Frey hairs in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29 g) for up to 6 sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest amount of force required to elicit a response was recorded as the PWT in grams.

[0227] Dynamic allodynia was assessed by lightly stroking the plantar surface of the hind paw with a cotton bud. Care was taken to perform this procedure in fully habituated rats that were not active to avoid recording general motor activity. At least three measurements were taken at each time point the mean of which represented the paw withdrawal latency (PWL). If no reaction was exhibited within 15 s the procedure was terminated and animals were assigned this withdrawal time. Thus 15 s effectively represents no withdrawal. A withdrawal response was often accompanied with repeated flinching or licking of the paw. Dynamic allodynia was considered to be present if animals responded to the cotton stimulus before 8 s of stroking.

RESULTS

Effect of Gabapentin and Sildenafil Alone on CCI-Induced Static and Dynamic Allodynia

[0228] Gabapentin dose-dependently (10-100 mg/kg, p.o.) blocked the maintenance of both static and dynamic allodynia with a minimum effective dose (MED) of 10 mg/kg (**FIGS. 1, 2**). The dose of 100 mg/kg produced a complete blockade of these responses. Sildenafil dose-dependently (10-30 mg/kg s.c.) blocked the maintenance of static allodynia with a minimum effective dose of 10 mg/kg and the dose of 30 mg/kg producing an approximate 60% blockade (**FIG. 1**). Sildenafil had a modest effect on the maintenance of dynamic allodynia with an MED of 30 mg/kg producing a 25% blockade (**FIG. 2**).

Effect of Combinations of Gabapentin and Sildenafil on CCI-Induced Static Allodynia

[0229] Gabapentin and sildenafil had peak antiallodynic actions at 2 h post administration in the CCI-induced static model. Thus, for clarity all combination data are expressed at this time point. Gabapentin and sildenafil were administered at fixed dose ratios of 1:10, 1:1, 10:1 and 20:1. Following fixed dose ratios of 1:10 and 20:1, combinations of gabapentin and sildenafil produced an additive interaction (**FIG. 3**). However, the fixed dose ratio of 1:1 and 10:1 demonstrated synergy with static allodynia completely blocked by a total dose of 20 mg/kg and 11 mg/kg respectively (**FIG. 3**). The 1:1 combination represents a 10-fold lower dose of gabapentin and 3-fold lower dose of sildenafil when administered alone whilst the 1:1 ratio represents a 10-fold lower dose of gabapentin and 30-fold lower dose of sildenafil when administered alone.

Effect of Combinations of Gabapentin and Sildenafil on CCI-Induced Dynamic Allodynia

[0230] Gabapentin and sildenafil had peak antiallodynic actions at 2 h post administration in the CCI-induced dynamic model. Thus, for clarity all combination data are expressed at this time point. Gabapentin and sildenafil were administered at fixed dose ratios of 1:10, 1:1, 10:1 and 20:1. Similar data were seen on dynamic allodynia to those with static allodynia. Following fixed dose ratios of 1:10 and 20:1, combinations of gabapentin and sildenafil produced an additive interaction (**FIG. 4**). However, the fixed dose ratio of 1:1 and 10:1 demonstrated synergy with static allodynia completely blocked by a total dose of 20 mg/kg and 11 mg/kg respectively. The 1:1 combination represents a 10-fold lower dose of gabapentin and 3-fold lower dose of sildenafil when administered alone whilst the 1:1 ratio represents a 10-fold lower dose of gabapentin and 30-fold lower dose of sildenafil when administered alone.

[0231] Similar experiments were also performed in the same model for a further alpha-2-delta ligand (pregabalin) in combination with sildenafil and also with gabapentin and a further PDEV inhibitor, 3-Ethyl-5-[5-(4-ethyl-piperazine-1-sulfonyl)-2-propoxy-phenyl]-2-pyridin-2-ylmethyl-2,6-dihydro-pyrazolo[4,3-d]pyrimidin-7-one (Compound AA). The results for these experiments are summarized below and in tabular form (table 1 & 2).

TABLE 1

Ratio Pregabalin:sildenafil	Pregabalin (mg/kg)	Sildenafil (mg/kg)	% reversal of allodynia	Total dose	Interaction
1:0	30	—	100	30	—
0:1	—	30	50	30	—
1:1	10	10	100	20	Synergy
10:1	10	1	100	11	Synergy

[0232]

TABLE 2

Ratio Gabapentin:Compound AA	Gabapentin (mg/kg)	Sildenafil (mg/kg)	% reversal of allodynia	Total dose	Interaction
1:0	100	—	100	100	—
0:1	—	30	50	30	—
10:1	10	1	100	11	Synergy

Effect of Combinations of Pregabalin and Sildenafil on CCI-Induced Static Allodynia

[0233] Pregabalin and sildenafil had peak antiallodynic actions at 2 h post administration in the CCI-induced static model. Pregabalin and sildenafil were administered at fixed dose ratios of 1:1 and 10:1. These fixed dose ratios demonstrated synergy with static allodynia completely blocked by a total dose of 20 mg/kg and 11 mg/kg respectively. The 1:1 combination represents a 3-fold lower dose of pregabalin and 3-fold lower dose of sildenafil when administered alone whilst the 1:1 ratio represents a 3-fold lower dose of pregabalin and 30-fold lower dose of sildenafil when administered alone.

Effect of Combinations of Gabapentin and Compound AA on CCI-Induced Static Allodynia

[0234] Gabapentin and Compound AA had peak antiallodynic actions at 2 h post administration in the CCI-induced static model. Gabapentin and Compound AA were administered at fixed dose ratios of 10:1. This fixed dose ratio demonstrated synergy with static allodynia completely blocked by a total dose of 11 mg/kg respectively. The the 1:1 ratio represents a 10-fold lower dose of gabapentin and 30-fold lower dose of Compound AA when administered alone.

[0235] Suitable PDEV inhibitors of the present invention may be prepared as described in the aforementioned patent literature references or are obvious to those skilled in the art on the basis of these documents.

[0236] Suitable alpha-2-delta ligand compounds of the present invention may be prepared as described herein below or in the aforementioned patent literature references or are obvious to those skilled in the art on the basis of these documents.

CHEMISTRY EXAMPLES

EXAMPLE 1

[0237] (3S,5R)-3-Amino-5-methyl-octanoic acid hydrochloride(R)-2,6-Dimethyl-non-2-ene

[0238] To (S)-citronellyl bromide (50 g, 0.228 mol) in THF (800 mL) at 0° C. was added LiCl (4.3 g) followed by $CuCl_2$ (6.8 g). After 30 minutes methylmagnesium chloride (152 mL of a 3 M solution in THF, Aldrich) was added and the solution warmed to room temperature. After 10 hours the solution was cooled to 0° C. and a saturated aqueous solution of ammonium chloride carefully added. The resultant two layers were separated and the aqueous phase extracted with ether. The combined organic phases were dried ($MgSO_4$) and concentrated to give (R)-2,6-dimethyl-non-2-ene. 32.6 g; 93%. Used without further purification. ^1H NMR (400 MHz; $CDCl_3$) δ 5.1 (m, 1H), 1.95 (m, 2H), 1.62 (s, 3H), 1.6 (s, 3H), 1.3 (m, 4H), 1.2 (m, 2H), 0.8 (s, 6H);^{13}C NMR (100 MHz; $CDCl_3$) □131.13, 125.28, 39.50, 37.35, 32.35, 25.92, 25.77, 20.31, 19.74, 17.81, 14.60.

[0239] (R)-4-Methyl-heptanoic acid. To (R)-2,6-dimethyl-non-2-ene (20 g, 0.13 mol) in acetone (433 mL) was added a solution of CrO_3 (39 g, 0.39 mol) in H_2SO_4 (33 mL)/H_2O (146 mL) over 50 minutes. After 6 hours a further amount of CrO_3 (26 g, 0.26 mol) in H_2SO_4 (22 mL)/H2O (100 mL) was added. After 12 hours the solution was diluted with brine and the solution extracted with ether. The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (gradient of 6:1 to 2:1 hexane/EtOAc) gave (R)-4-methyl-heptanoic acid as an oil. 12.1 g; 65%. MS, m/z (relative intensity): 143 [M−H, 100%].

(4R,5S)-4-Methyl-3-((R)-4-methyl-heptanoyl)-5-phenyl-oxazolidin-2-one

[0240] To (R)-4-methyl-heptanoic acid (19 g, 0.132 mol) and triethylamine (49.9 g, 0.494 mol) in THF (500 mL) at 0° C. was added trimethylacetylchloride (20 g, 0.17 mol). After 1 hour LiCl (7.1 g, 0.17 mol) was added followed by (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone) 3 (30 g, 0.17 mol). The mixture was warmed to room temperature and after 16 hours the filtrate was removed by filtration and the solution concentrated under reduced pressure. Flash chromatography (7:1 hexane/EtOAc) gave (4R,5S)-4-methyl-3-((R)-4-methyl-heptanoyl)-5-phenyl-oxazolidin-2-one as an oil. 31.5 g; 79%. $[\alpha]_D$=+5.5 (c 1 in $CHCl_3$). MS, m/z (relative intensity): 304 [M+H, 100%].

[0241] (3S,5R)-5-Methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester. To (4R,5S)-4-methyl-3-((R)-4-methyl-heptanoyl)-5-phenyl-oxazolidin-2-one (12.1 g, 0.04 mol) in THF (200 ml) at −50° C. was added sodium bis(trimethylsilyl)amide (48 mL of a 1 M solution in THF). After 30 min t-butylbromoaceate (15.6 g, 0.08 mol) was added. The solution was stirred for 4 hours at −50° C. and then warmed to room temperature. After 16 hours a saturated aqueous solution of ammonium chloride was added and the two layers separated. The aqueous phase was extracted with ether and the combined organic phases dried ($MgSO_4$) and concentrated. Flash chromatography (9:1 hexane/EtOAc) gave (3S,5R)-5-methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester as a white solid 12 g; 72%. $[\alpha]_D$=+30.2 (c 1 in $CHCl_3$). ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.47, 171.24, 152.72, 133.63, 128.87, 125.86, 80.85, 78.88, 55.34, 39.98, 38.77, 38.15, 37.58, 30.60, 28.23, 20.38, 20.13, 14.50, 14.28.

[0242] (S)-2-((R)-2-Methyl-pentyl)-succinic acid 4-tert-butyl ester. To (3S,5R)-5-methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester (10.8 g, 0.025 mol) in H_2O (73 mL) and THF (244 mL) at 0° C. was added a premixed solution of LiOH (51.2 mL of a 0.8 M solution) and H_2O_2 (14.6 mL of a 30% solution). After 4 hours a further 12.8 mL LiOH (0.8 M solution) and 3.65 mL of H_2O_2 (30% solution) was added. After 30 minutes sodium bisulfite (7 g), sodium sulfite (13 g), and water (60 mL) was added followed by hexane (100 mL) and ether (100 mL). The two layers were separated and

the aqueous layer extracted with ether. The combined organic phases were concentrated to an oil that was dissolved in heptane (300 mL). The resultant solid was filtered off and the filtrate dried ($MgSO_4$) and concentrated to afford (S)-2-((R)-2-methyl-pentyl)-succinic acid 4-tert-butyl ester (6 g, 93%) which was used immediately without further purification. MS, m/z (relative intensity): 257 [M+H, 100%].

[0243] (3S, 5R)-3-Benzyoxycarbonylamino-5-methyl-octanoic acid, tert-butyl ester. A solution of (S)-2-((R)-2-methyl-pentyl)-succinic acid 4-tert-butyl ester (6.0 g, 23.22 mmol) and triethylamine (3.64 mL, 26.19 mmol) in toluene (200 mL) was treated with diphenylphosphoryl azide (5.0 mL, 23.22 mL) and stirred at room temperature for 0.5 hours. After the reaction mixture was then heated at reflux for 3 h and cooled briefly, benzyl alcohol was added (7.2 mL, 69.7 mmol) and the solution heated for another 3 h. After the reaction mixture was allowed to cool, it was diluted with ethyl ether (200 mL) and the combined organic layer was washed successively with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The concentrated organic component was purified by chromatography (MPLC) eluting with 8:1 hexanes: ethyl acetate to provide (3S, 5R)-3-benzyoxycarbonylamino-5-methyl-octanoic acid, tert-butyl ester (6.4 g, 75.8%). MS: M+1: 364.2, 308.2.

[0244] (3S, 5R)-3-Amino-5-methyl-octanoic acid, tert-butyl ester. A solution of (3S, 5R)-3-benzyoxycarbonylamino-5-methyl-octanoic acid, tert-butyl ester (2.14 g, 5.88 mmol) in THF (50 mL) was treated with Pd/C (0.2 g) and H_2 at 50 psi for 2 hours. The reaction mixture was then filtered and concentrated to an oil in vacuo to give (3S, 5R)-3-amino-5-methyl-octanoic acid, tert-butyl ester in quantitative yield. MS: M+1: 230.2, 174.1.

[0245] (3S, 5R)-3-Amino-5-methyl-octanoic acid hydrochloride. A slurry of (3S, 5R)-amino-5-methyl-octanoic acid, tert-butyl ester (2.59 g, 11.3 mmol) in 6N HCl (100 mL) was heated under reflux 18 hours, cooled, and filtered over Celite. The filtrate was concentrated in vacuo to 25 mL and the resulting crystals were collected and dried to provide (3S, 5R)-3-amino-5-methyl-octanoic acid hydrochloride, mp 142.5-142.7° C. (1.2 g, 50.56%). A second crop (0.91 g) was obtained from the filtrate. Anal. Calc'd for $C_9H_{19}NO_2$.HCl: C, 51.55; H, 9.61; N, 6.68; Cl, 16.91. Found: C, 51.69; H, 9.72; N, 6.56; Cl, 16.63.

[0246] (3S, 5R)-3-Amino-5-methyl-octanoic acid hydrochloride acid salt. 5.3 g of 2S-(2R-methyl-pentyl)-succinic acid-4-tert-butyl ester contained in 30 mL methyltertbutyl ether is reacted at room temperature with 3.5 mL triethylamine followed by 6.4 g of diphenylphosphoryl azide. After allowing the reaction to exotherm to 45° C. and stirring for at least 4 hours, the reaction mixture is allowed to cool to room temperature and stand while the phases separated. The lower layer is discarded and the upper layer is washed with water, followed by dilute aqueous HCl. The upper layer is then combined with 10 mL of 6 N aqueous HCl, and stirred at 45-65° C. The reaction mixture is concentrated by vacuum distillation to about 10-14 mL and allowed to crystallize while cooling to about 5° C. After collecting the product by filtration, the product is washed with toluene and reslurried in toluene. The product is dried by heating under vacuum resulting in 2.9 g (67%) of white crystalline product. The product may be recrystallized from aqueous HCl. mp 137° C., HNMR (400 MHz, D6 DMSO) δ 0.84-0.88 (overlapping d and t, 6H), 1.03-1.13 (m, 1H), 1.16-1.37 (m,4H), 1.57-1.68 (m, 2H), 2.55 (dd, 1H, J=7, 17 Hz), 2.67 (dd, 1H, J=6, 17 Hz), 3.40 (m, 1H), 8.1 (br s, 3H), 12.8 (br s, 1H).

EXAMPLE 2

(3S, 5R)-Amino-5-methyl-heptanoic acid

[0247] Methanesulfonic acid (S)-3,7-dimethyl-oct-6-enyl ester. To S-(−)-citronellol (42.8 g, 0.274 mol) and triethylamine (91 mL, 0.657 mol) in CH_2Cl_2 (800 mL) at 0° C. was added methanesulphonyl chloride (26 mL, 0.329 mol) in CH_2Cl_2 (200 mL). After 2 hours at 0° C. the solution was washed with 1N HCl then brine. The organic phase was dried ($MgSO_4$) and concentrated to afford the titled compound an oil (60.5 g, 94%) which was used without further purification. MS, m/z (relative intensity): 139 [100%], 143 [100%].

[0248] (R)-2,6-Dimethyl-oct-2-ene. To methanesulfonic acid (S)-3,7-dimethyl-oct-6-enyl ester (60 g, 0.256 mol) in THF (1 L) at 0° C. was added lithium aluminum hydride (3.8 g, 0.128 mol). After 7 hours, a further 3.8 g of lithium aluminum hydride was added and the solution warmed to room temperature. After 18 hours, a further 3.8 g of lithium aluminum hydride was added. After a further 21 hours, the reaction was carefully quenched with 1N citric acid and the solution diluted further with brine. The resultant two phases were separated and the organic phase was dried ($MgSO_4$) and concentrated to afford the titled compound as an oil which was used without further purification. MS, m/z (relative intensity): 139 [M+H, 100%].

[0249] (R)-4-Methyl-hexanoic acid. A procedure similar to the synthesis of (R)-4-methyl-heptanoic acid was utilized giving the acid as an oil (9.3 g, 56%). IR (film) 2963, 2931, 2877, 2675, 1107, 1461, 1414 cm^{-1}; MS, m/z (relative intensity): 129 [M−H, 100%].

[0250] (4R,5S)-4-Methyl-3-((R)-4-methyl-hexanoyl)-5-phenyl-oxazolidin-2-one. A procedure similar to the synthesis of (4R,5S)-4-methyl-3-((R)-4-methyl-heptanoyl)-5-phenyl-oxazolidin-2-one was utilized giving the titled compound as an oil (35.7 g, 95%). MS, m/z (relative intensity): 290 [M+H, 100.

[0251] (3S,5R)-5-Methyl-3-[1-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidin-3-yl)-methanoyl]-heptanoic acid tert-butyl ester. A procedure similar to the preparation of (3S, 5R)-5-methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester was followed giving the titled compound as an oil (7.48 g; 31%). MS, m/z (relative intensity): 178 [100%], 169 [100%]; $[\alpha]_D$=+21.6 (c 1 in $CHCl_3$).

[0252] (S)-2-((R)-2-Methyl-butyl)-succinic acid 4-tert-butyl ester. (3S,5R)-5-Methyl-3-[1-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidin-3-yl)-methanoyl]-heptanoic acid tert-butyl ester (7.26 g, 0.018 mol) in H_2O (53 mL) and THF (176 mL) at 0° C. was added a premixed solution of LiOH (37 mL of a 0.8 M solution) and H_2O_2 (10.57 mL of a 30% solution) and the solution warmed to room temperature. After 2 hours sodium bisulfite (7 g), sodium sulfite (13 g), and water (60 mL) was added and the two layers were separated and the aqueous layer extracted with ether. The combined organic phases were concentrated to an oil that was dissolved in heptane (200 mL). The resultant solid was

filtered off and the filtrate dried ($MgSO_4$) and concentrated to afford the titled compound as an oil (4.4 g) that was used without further purification. MS, m/z (relative intensity): 243 [100%].

[0253] (3S, 5R)-3-Benzyoxycarbonylamino-5-methyl-heptanoic acid, tert-butyl ester—This compound was prepared as described above starting with (S)-2-((R)-2-methyl-butyl) succinic acid, 4-tert-butyl ester to give (3S, 5R)-3-benzyoxycarbonylamino-5-methyl-heptanoic acid, tert-butyl ester as an oil (73.3% yield). ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.84(t, 3H, J=7.33 Hz), 0.89(d, 3H, J=6.60 Hz), 1.12-1.38 (m, 4H), 1.41 (s, 9H), 1.43-1.59 (m, 2H), 2.42 (m, 2H), 4.05 (m, 1H), 5.07 (t, 2H J=12.95 Hz), and 7.28-7.34 (m, 5H).

[0254] (3S, 5R)-Amino-5-methyl-heptanoic acid, tert-butyl ester—This compound was prepared as described above starting with (3S, 5R)-3-benzyoxycarbonylamino-5methyl-heptanoic acid, tert-butyl ester instead of (3S, 5R)-3-benzyoxycarbonylamino-5-methyl-octanoic acid, tert-butyl ester to give the titled compound. ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.84 (overlapping t and d, 6H), 1.08-1.16(m, 2H), 1.27-1.30(m, 2H), 1.42(s, 9H), 1.62 (br s, 2H), 2.15 (dd, 1H, J=8.54 and 15.62 Hz), 2.29(dd, 1H, J=4.15 and 15.37 Hz), and 3.20(br s, 2H).

[0255] (3S, 5R)-Amino-5-methyl-heptanoic acid hydrochloride—A slurry of (3S, 5R)-amino-5-methyl-heptanoic acid, tert-butyl ester (1.44 g, 6.69 mmol) in 3N HCl was heated at reflux for 3 hours, filtered hot over Celite, and concentrated to dryness. Trituration of the resulting solid in ethyl ether provided (3S, 5R)-3-amino-5-methyl-heptanoic acid hydrochloride, (0.95 g, 85%) mp 126.3-128.3° C. Anal. Calc'd for $C_8H_{17}NO_2.HCl.0.1H_2O$: C, 48.65; H, 9.29; N, 7.09; Cl, 17.95. Found: C, 48.61; H, 9.10; N, 7.27; Cl, 17.87MS: M+1: 160.2

EXAMPLE 3

(3S, 5R)-3-Amino-5-methyl-nonanoic acid

[0256] (R)-4-Methyl-octanoic acid. Lithium chloride (0.39 g, 9.12 mmol) and copper (I) chloride (0.61 g, 4.56 mmol) were combined in 45 ml THF at ambient temperature and stirred 15 minutes, then cooled to 0° C. at which time ethylmagnesium bromide (1 M solution in THF, 45 mL, 45 mmol) was added. (S)-citronellyl bromide (5.0 g, 22.8 mmol) was added dropwise and the solution was allowed to warm slowly to ambient temperature with stirring overnight. The reaction was quenched by cautious addition of sat. NH_4Cl (aq), and stirred with Et_2O and sat. NH_4Cl (aq) for 30 minutes. The phases were separated and the organic phase dried ($MgSO_4$) and concentrated. The crude (R)-2,6-dimethyl-dec-2-ene was used without purification. To a solution of (R)-2,6-dimethyl-dec-2-ene (3.8 g, 22.8 mmol) in 50 mL acetone at 0° C. was added Jones' reagent (2.7 M in H_2SO_4 (aq), 40 mL, 108 mmol) and the solution was allowed to warm slowly to ambient temperature with stirring overnight. The mixture was partitioned between Et_2O and H_2O, the phases were separated, and the organic phase washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (8:1 hexanes:EtOAc) to afford 2.14 g (59%) of the titled compound as a colorless oil: LRMS: m/z 156.9 (M+). Jones' reagent was prepared as a 2.7M solution by combining 26.7 g CrO_3, 23 mL H_2SO_4, and diluting to 100 mL with H_2O.

[0257] (4R, 5S)-4-Methyl-3-((R)-4-methyl-octanoyl)-5-phenyl-oxazolidin-2-one. To (R)-4-methyl-octanoic acid (2.14 g, 13.5 mmol) in 25 mL CH_2Cl_2 at 0° C. was added 3 drops DMF, followed by oxalyl chloride (1.42 mL, 16.2 mmol) resulting in vigorous gas evolution. The solution was warmed directly to ambient temperature, stirred 30 minutes, and concentrated. Meanwhile, to a solution of the oxazolidinone (2.64 g, 14.9 mmol) in 40 mL THF at −78° C. was added n-butyllithium (1.6 M soln in hexanes, 9.3 mL, 14.9 mmol) dropwise. The mixture was stirred for 10 minutes at which time the acid chloride in 10 mL THF was added dropwise. The reaction was stirred 30 minutes at −78° C., then warmed directly to ambient temperature and quenched with sat. NH_4Cl. The mixture was partitioned between Et_2O and sat. NH_4Cl (aq), the phases were separated, and the organic phase dried ($MgSO_4$), and concentrated to furnish 3.2 g of the titled compound as a colorless oil. LRMS: m/z 318.2 (M+).

[0258] (3S,5R)-5-Methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-nonanoic acid tert-butyl ester. To a solution of diisopropylamine (1.8 mL, 12.6 mmol) in 30 mL THF at −78° C. was added n-butyllithium (1.6 M soln in hexanes, 7.6 mL, 12.1 mmol), and the mixture stirred 10 minutes at which time (4R, 5S)-4-Methyl-3-((R)-4-methyl-octanoyl)-5-phenyl-oxazolidin-2-one (3.2 g, 10.1 mmol) in 10 mL THF was added dropwise. The solution was stirred for 30 minutes, t-butyl bromoacetate (1.8 mL, 12.1 mmol) was added quickly dropwise at −50° C., and the mixture was allowed to warm slowly to 10° C. over 3 hours. The mixture was partitioned between Et_2O and sat. NH_4Cl (aq), the phases were separated, and the organic phase dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (16:1 to 8:1 hexanes:EtOAc) to provide 2.65 g (61%) of the titled compound as a colorless crystalline solid, mp=84-86° C. $[\delta]_D^{23}$+17.1 (c=1.00, $CHCl_3$).

[0259] (S)-2-((R)-2-Methyl-hexyl)-succinic acid 4-tert-butyl ester. To a solution of (3S,5R)-5-Methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-nonanoic acid tert-butyl ester (2.65 g, 6.14 mmol) in 20 mL THF at 0° C. was added a precooled (0° C.) solution of LiOH monohydrate (1.0 g, 23.8 mmol) and hydrogen peroxide (30 wt % aqueous soln, 5.0 mL) in 10 mL H_2O. The mixture was stirred vigorously for 90 minutes, then warmed to ambient temperature and stirred 90 minutes. The reaction was quenched at 0° C. by addition of 100 mL 10% $NaHSO_3$ (aq), then extracted with Et_2O. The phases were separated, and the organic phase washed with brine, dried ($MgSO_4$), and concentrated. The titled compound was used without purification.

[0260] (3S, 5R)-3-Benzyoxycarbonylamino-5-methyl-nonanoic acid, tert-butyl ester—This compound was prepared similarly as described above starting with (S)-2-((R)-2-methylhexyl) succinic acid, 4-tert-butyl ester instead of (S)-2-((R)-2-methylpentyl) succinic acid, 4-tert-butyl ester to provide the titled compound as an oil (71.6% yield). ^{1}HNMR (400 MHz; $CDCl_3$) δ 0.81(t, 3H, J=4.40 Hz), 0.85(d, 3H, J=6.55 Hz), 1.06-1.20(m, 7H), 1.36(s, 9H), 1.38-1.50(m, 2H), 2.36(m, 2H), 3.99(m, 1H), 5.02(m+s, 3H), and 7.28-7.28(m, 5H).

[0261] (3S, 5R)-3-Amino-5-methyl-nonanoic acid, tert-butyl ester—This compound was prepared as described

above starting with (3S, 5R)-benzyoxycarbonylamino-5-methyl-nonanoic acid, tert-butyl ester instead of (3S, 5R)-3-benzyoxycarbonylamino-5-methyl-octanoic acid, tert-butyl ester. Yield=97%. ^{1}HNMR (400 MHz; $CDCl_3$) δ 0.82(overlapping d and t, 6H), 1.02-1.08(m, 1H), 1.09-1.36(m, 6H), 1.39(s, 9H), 1.47(brs, 1H), 1.80(s, 2H), 2.13(dd, 1H, J=8.54 and 15.61 Hz), and 2.27(dd, 1H, J=4.15 and 15.38 Hz).

[0262] (3S, 5R)-3-Amino-5-methyl-nonanoic acid hydrochloride—A mixture of (3S, 5R)-3-amino-5-methyl-nonanoic acid, tert-butyl ester (1.50 g, 6.16 mmol) in 3N HCl (100 mL) was heated at reflux for 3 hours, filtered hot over Celite, and concentrated to 30 mL in vacuo. The resulting crystals were collected, washed with additional 3N HCl, and dried to provide the title compound, mp 142.5-143.3° C. Additional crops were obtained from the filtrate to provide 1.03 g (70.4%). Anal. Calc'd for $C_{10}H_{21}NO_2$.HCl: C, 53.68; H, 9.91; N, 6.26; Cl, 15.85; Found: C, 53.89; H, 10.11; N, 6.13; MS: M+1: 188.1.

EXAMPLE 4

(2R, 4R)-2-Aminomethyl-4-methyl-heptanoic acid

[0263] 5R-Methyl-3R-(4S-methyl-2-oxo-5R-phenyloxazolidine-3-carbonyl)octanoic acid. A solution of (3R,5R)-5-Methyl-3-((4S,5R)-4-methyl-2oxo-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester(3.9 g, 9.34 mmol) in dichloromethane (150 mL) was treated with trifluoroacetic acid (7.21 mL, 93.4 mL) and stirred 18 hours at ambient temperature. After the solvents and reagent were removed in vacuo, the resulting residue was tritrurated in 100 mL hexanes to provide 3.38 g of the title compound (100%) mp 142-143° C.

[0264] [4R-Methyl-2R-(4S-methyl-2-oxo-5R-phenyloxazolidine-3-carbonyl)heptyl]carbamic acid benzyl ester. A solution of 5R-methyl-3R-(4S-methyl-2-oxo-5R-phenyloxazolidine-3-carbonyl)octanoic acid (1.98 g, 5.48 mmol) and triethylamine (0.92 mL, 6.57 mmol) was treated with diphenylphosphorylazide (1.2 mL, 5.48 mmol), stirred 30 min at ambient temperature and then heated at reflux for 3 hours. After cooling briefly, the reaction mixture was treated with benzyl alcohol (2.8 mL, 27.4 mmol) and heated for an additional 3 h at reflux. The reaction mixture was cooled, diluted with ethyl ether (150 mL), washed successively with sat'd $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo to an oil. Chromatography (MPLC, elution with 4:1 hexanes:ethyl acetate) provided the title compound (2.0 g, 78.3%) as an oil. MS M+1=467.1.

[0265] 2R-(Benzyloxycarbonylaminomethyl)-4R-methyl-heptanoic acid. A solution of 4R-methyl-2R-(4S-methyl-2-oxo-5R-phenyloxazolidine-3-carbonyl)heptyl]carboamic acid benzyl ester (4.12 g, 8.83 mmol) in 3:1 THF:water (100 mL) was cooled to 0° C. and treated with a mixture of 0.8 N LiOH (17.5 mL, 14 mmol) and 30% H_2O_2 (4.94 mL, 44 mmol). After the reaction mixture was stirred in the cold 3 hours, it was quenched with a slurry of $NaHSO_3$ (2.37 g) and Na_2SO_3 (4.53 g) in water (30 mL) and stirred 1 hour. The reaction mixture was diluted with ethyl ether (200 mL), partitioned, and the organic layer washed with brine and dried ($MgSO_4$). The concentrated organic extract was chromatographed (MPLC) eluting with ethyl acetate to give 1.25 g of 2R-(benzyloxycarbonylaminomethyl)-4R-methylheptanoic acid (46%). MS M+1=308.1.

[0266] (2R,4R)-2-Amino-4-methyl-heptanoic acid hydrochloride. A mixture of 2R-(benzyloxycarbonylaminomethyl)-4R-methyl-heptanoic acid (1.25 g, 4.07 mmol) and Pd/C (20%, 0.11 g) in methanol (50 mL) was hydrogenated at 50 psi for 18 hours. After the catalyst was removed by filtration, the solvent was removed in vacuo and the resulting solid triturated in ether to provide (2S, 4R)-2-amino-4-methyl-heptanoic acid hydrochloride (0.28 g, 40%) mp 226.3-228.0° C. MS M+1=174.0. Anal. Calc'd for $C_9H_{19}NO_2$.0.1 H_2O C, 61.75; H, 11.06; N, 8.00; Found C, 61.85; H, 10.83; N, 8.01.

EXAMPLE 5

2-Aminomethyl-4,4-dimethyl-heptanoic acid hydrochloride

[0267] 2-Cyano-4,4-dimethyl-hepta-2,6-dienoic acid ethyl ester. A solution of 2,2-dimethyl-pent-4-enal (5.0 g, 44 mmol), cyano-acetic acid ethyl ester (5.12 mL, 48 mmol), piperidine (1.3 mL, 14 mmol) and acetic acid (4.52 mL, 80 mmol) in 170 mL of toluene was heated under reflux for 18 hours in a flask equipped with a Dean-Stark separator. Several mL of water was collected in the trap. The reaction was cooled and washed with 1N HCl, $NaHCO_3$ and brine, successively. The organic layers were dried over Na_2SO_4 and concentrated to an oil. This oil was chromatographed eluting with 20% of EtOAc in hexane to give a combination of two lots total 8.3 g (91%). ^{1}H NMR (400 MHz; $CDCl_3$) 1.28 (s, 6H), 1.32 (t, 3H, J=7 Hz),. 2.26 (d, 2H, J=7.6 Hz), 4.27 (q, 2H, J=7.2 Hz), 5.08 (d, 1H, J=12 Hz), 5.10 (d, 1H, J=4 Hz), 5.72 (m, 1H).

[0268] 2-Aminomethyl-4,4-dimethyl-heptanoic acid hydrochloride. 2-Cyano-4,4-dimethyl-hepta-2,6-dienoic acid ethyl ester (5.88 g, 28 mmol) was dissolved in the mixture of 91 mL of ethanol and 6 mL of HCl and treated with 0.4 g of PtO_2. The reaction was carried out under 100 psi of hydrogen pressure at room temperature for 15 hours. The catalyst was filtered and filtrate was concentrated to give 3.8 g of the desired product 2-aminomethyl-4,4-dimethyl-heptanoic acid ethyl ester as an oil. MS (APCI): 216.2 $(M+1)^+$. This oil was refluxed in 75 mL of 6N HCl for 18 hours. While the reaction was cooled, a precipitate formed. The solid was filtered, washed with additional HCl solution and triturated with ether to give the clean title compound. MS (APCI): 188.1 $(M+1)^+$. 186.1 $(M-1)^+$. ^{1}H NMR (400 MHz; CD_3OD): 0.91 (9H, m), 1.30 (5H, m), 1.81 (dd, 1H, J=7.2 Hz, 14.4 Hz), 2.72 (1H, m), 3.04 (2H, m); Anal. Calc'd for $C_{10}H_{21}NO_2$.HCl: C, 53.68; H, 9.91; N, 6.26; Cl, 15.85; Found: C, 53.83; H, 10.15; N, 6.22; Cl, 15.40; MP: 229.5-231.0° C.

EXAMPLE 6

(S)-3-Amino-5,5-dimethyl-octanoic acid

[0269] 3-(4,4-Dimethyl-heptanoyl)-(R)-4-methyl-(S)-5-phenyl-oxazolidin-2-one: A solution of 4,4-dimethyl-heptanoic acid (1.58 g, 10 mmol) and triethylamine (4.6 mL) in 50 mL THF was cooled to 0° C. and treated with 2,2-dimethyl-propionyl chloride (1.36 mL). After one hour, 4R-methyl-5S-phenyl-oxazolidin-2-one (1.95 g, 11 mmol) and lithium chloride (0.47 g, 11 mmol)was added and the mixture was stirred for 18 hours. The precipitate was filtered and washed thoroughly with additional THF. The filtrate was

concentrated in vacuo to give an oily solid. This solid was dissolved in 200 mL Et_2O, washed successively with saturated $NaHCO_3$, 0.5N HCl and saturated NaCl, dried ($MgSO_4$) and concentrated in vacuo to give the title compound as an oil (3.0 g, 95%). ^{1}HNMR (400 MHz; $CDCl_3$): 0.73-0.84 (m, 12H), 1.10-1.22 (m, 4H), 1.46-1.54 (m, 2H), 2.75-2.87 (m, 2H), 4.70 (m, 1H, J=7 Hz), 5.59 (d, 1H, J=7 Hz), 7.22-7.37 (m, 5H).

[0270] 5,5-Dimethyl-(S)-3-((R)-4-methyl-2-oxo-(S)-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester: According to example 1, 5.07 g (16 mmol) of 3-(4,4-dimethyl-heptanoyl)-4-methyl-5-phenyl-oxazolidin-2-one, 18 mL (1N, 18 mmol) of NaHMDS solution and 4.72 mL (32 mmol) of bromo-acetic acid tert-butyl ester gave 3.40 g (49.3%) of the title compound as a crystalline solid. m.p.: 83-85° C.

[0271] (S)-2-(2,2-Dimethyl-pentyl)-succinic acid 4-tert-butyl ester: According to example 1, 3.4 g (7.9 mmol) of 5,5-dimethyl-3-(4-methyl-2-oxo-5-phenyl-oxazolidine-3-carbonyl)-octanoic acid tert-butyl ester, 16 mL (12.8 mmol) of 0.8N LiOH and 4.5 mL of 30% H_2O_2 gave 2.42 g (>100%) of the title compound as an oil. ^{1}HNMR (400 MHz; $CDCl_3$): 0.77-0.82 (m, 9H), 1.14-1.29 (m, 5H), 1.42 (s, 9H), 1.77 (dd, 1H, J=8 Hz, 16 Hz), 2.36 (dd, 1H, J=6 Hz, 16 Hz), 2.59 (dd, 1H, J=8 Hz, 16 Hz), 2.75-2.85 (m, 1H).

[0272] (S)-3-Benzyloxycarbonylamino-5,5-dimethyl-octanoic acid tert-butyl ester: According to example 1, 2.14 g (7.9 mmol)of 2-(2,2-dimethyl-pentyl)-succinic acid 4-tert-butyl ester, 1.7 mL of DPPA, 1.1 mL of Et_3N and 2.44 mL of BnOH provided 1.63 g (54.8% in two steps) of the title compound as an oil. ^{1}HNMR (400 MHz; $CDCl_3$): 0.78-0.89 (m, 9H), 1.10-1.30 (m, 5H), 1.36 (s, 9H), 2.39 (t, 2H, J=5 Hz), 4.95-4.05 (m, 1H), 5.00 (s, 2H), 5.09 (d, 1 H, J=9.6 Hz), 7.22-7.30 (m, 5H).

[0273] (S)-3-Amino-5,5-dimethyl-octanoic acid tert-butyl ester: According to example 1, 1.63 g of 3-benzyloxycarbonylamino-5,5-dimethyl-octanoic acid tert-butyl ester and 0.2 g of 20% Pd/C furnished the title compound. MS, m/z, 244.2 $(M+12)^+$.

[0274] (S)-3-Amino-5,5-dimethyl-octanoic acid hydrochloride: According to example 1,3-amino-5,5-dimethyl-octanoic acid tert-butyl ester was treated with 3N HCl to provide 286 mg of the title compound as a solid. MS (APCI), m/z: 188.1 $(M+1)^+$. 186.1 $(M-1)^+$. Anal. Calc'd for $C_{10}H_{21}NO_2.HCl.0.12H_2O$: C, 53.17; H, 9.92; N, 6.20; Cl, 15.69; Found: C, 53.19; H, 10.00; N, 6.08; Cl, 15.25. α=+20° (MeOH). MP: 194.2-195.2° C.

EXAMPLE 7

2-Aminomethyl-3-(1-methyl-cyclopropyl)-propionic acid

[0275] 2-Cyano-3-(1-methyl-cyclopropyl)-acrylic acid ethyl ester. To 1-methylcyclopropane-methanol (Aldrich, 1.13 mL, 11.6 mmol) in 50 mL CH_2Cl_2 was added neutral alumina (2.5 g) and then PCC (2.5 g, 11.6 mmol), and the mixture stirred 3 h at ambient temperature. The mixture was filtered through a 1 cm plug of silica gel under vacuum, and rinsed with Et_2O. The filtrate was concentrated to ca. 5 mL total volume. To the residue was added THF (10 mL), ethyl cyanoacetate (1.2 mL, 11.3 mmol), piperidine (5 drops), and finally acetic acid (5 drops). The whole was stirred at ambient temperature overnight, then partitioned between Et_2O and sat. aq. $NaHCO_3$. The phases were separated and the organic phase washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (10→15% EtOAc/hexanes) provided 0.53 g (25%) of the ester as a colorless oil that crystallized on standing. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.86; H, 7.47; N, 7.70.

[0276] 2-Aminomethyl-3-(1-methyl-cyclopropyl)-propionic acid ethyl ester. To 2-cyano-3-(1-methyl-cyclopropyl)-acrylic acid ethyl ester (0.45 g, 2.5 mmol) in 16 mL EtOH:THF (1:1) was added RaNi (0.4 g), and the mixture was hydrogenated in a Parr shaker at 48 psi for 15.5 h. Pearlman's catalyst (0.5 g) was then added and hydrogenation was continued for an additional 15 h. The mixture was filtered and concentrated. Flash chromatography of the residue 2→3→4→5→6→8% MeOH/CH_2Cl_2 provided 0.25 g (54%) of the aminoester as a colorless oil. LRMS: m/z 186.1 (M+1).

[0277] 2-Aminomethyl-3-(1-methyl-cyclopropyl)-propionic acid. To a solution of 2-aminomethyl-3-(1-methyl-cyclopropyl)-propionic acid ethyl ester (0.25 g, 1.35 mmol) in 10 mL methanol at 0° C. was added 10% aq. NaOH (10 mL). The mixture was stirred at ambient temperature overnight, then concentrated to remove the methanol. The residue was cooled to 0° C. and acidified to pH 2 with conc. HCl. After allowing to warm to ambient temperature the mixture was loaded onto DOWEX-50WX8-100 ion exchange resin and eluted with H_2O until neutral to litmus. Elution was continued with 5% aq. NH_4OH (100 mL) and the alkaline fractions concentrated to provide 0.15 g (71%) of the amino acid as a colorless solid. LRMS: m/z 158.0 (M+1).

EXAMPLE 8

(3S,5R)-3-Amino-5-methyl-octanoic acid

[0278] (5S)-5-Methyl-octa-2,6-dienoic acid tert-butyl ester. To a solution of (S)-3-methyl-hex-4-enoic acid ethyl ester* (1.0 g, 6.4 mmol) in 30 mL toluene at −78° C. was added DIBAH (1.0M in THF, 6.4 mL) dropwise over 5 min. The mixture was stirred at −78° C. 45 min at which time 5 drops of methanol were added, resulting in vigorous H_2 evolution. Methanol was added until no more gas evolution was observed (ca. 5 mL). At this time the cold bath was removed and ca. 5 mL of sat. aq. Na^+K^+ tartrate was added. When the mixture reached room temperature, additional sat. aq. Na^+K^+ tartrate and Et_2O were added and stirring was continued until the phases were mostly clear (ca. 1 h). The phases were separated, and the organic phase washed with brine, dried ($MgSO_4$), and concentrated to ca. 10 mL total volume owing to volatility concerns. The crude mixture was combined with an additional batch of aldehyde prepared from 10 mmol of the ester by the method described above and the whole used without purification. To a suspension of sodium hydride (60% dispersion in mineral oil) in 25 mL THF was added t-butyl-P,P-dimethylphosphonoacetate (3.0 mL, 15 mmol) dropwise over 1 h such that the evolution of H_2 was under control. After the addition was complete, the crude aldehyde in toluene (ca. 20 mL total volume) was added quickly dropwise and the mixture stirred at ambient temperature overnight. The mixture was partitioned between

Et_2O and sat. aq. NH_4Cl, the phases separated, the organic phase washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (0→3→5% EtOAc/hexanes) afforded 1.0 g (29%, two steps) of the unsaturated ester as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 6.75 (m, 1H), 5.66 (m, 1H), 5.30 (m, 2H), 2.03-2.29 (m, 3H), 1.58 (d, J=6.1 Hz, 3H), 1.41 (s, 9H), 0.91 (d, J=6.6 Hz, 3H).

[0279] *(S)-3-methyl-hex-4-enoic acid ethyl ester was prepared from (S)-trans-3-Penten-2-ol [Liang, J.; Hoard, D. W.; Van Khau, V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem.*, 1999, 64, 1459] via Johnson-Claisen rearrangement with triethylorthoacetate according to the literature protocol [Hill, R. K.; Soman, R.; Sawada, S., *J. Org. Chem.*, 1972, 37, 3737].

[0280] (3R,5S)-3-[Benzyl-(1-phenyl-ethyl)-amino]-5-methyl-oct-6-enoic acid tert-butyl ester. To a solution of (S)-(−)-N-benzyl-α-methylbenzylamine (0.60 mL, 2.85 mmol) in 9.0 mL THF at −78° C. was added n-butyllithium (1.6M in hexanes, 1.6 mL) quickly dropwise resulting in a deep pink color. The mixture was stirred at −78° C. for 30 min at which time (5S)-5-Methyl-octa-2,6-dienoic acid tert-butyl ester (0.5 g, 2.38 mmol) in 1.0 mL THF was added slowly dropwise, resulting in a pale tan color which darkened over 3 h. The mixture was stirred 3 h at −78° C., then quenched with sat. aq. NH_4Cl. The mixture was allowed to warm to rt and stirred overnight, then partitioned between EtOAc and sat. aq. NH_4Cl. The phases were concentrated, and the organic phase dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (3→5% EtOAc/hexanes) provided 0.52 g (52%) of the aminoester as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.34 (m, 2H), 7.20 (m, 8H), 5.27 (m, 2H), 3.74 (m, 1H), 3.72 (d, J=15.9 Hz, 1H), 3.41 (d, J=14.9 Hz, 1H), 3.27 (m, 1H), 2.38 (m, 1H), 1.98 (dd, J=3.7, 14.2 Hz, 1H), 1.81 (dd, J=9.3, 14.4 Hz, 1eH), 1.54 (d, J=4.9 Hz, 3H), 1.32 (s, 9H), 1.24 (d, J=7.1 Hz, 3H), 0.99 (m, 2H), 0.74 (d, J=6.6 Hz, 3H).

[0281] (3S,5R)-3-Amino-5-methyl-octanoic acid. To a solution of (3R,5S)-3-[Benzyl-(1-phenyl-ethyl)-amino]-5-methyl-oct-6-enoic acid tert-butyl ester (0.92 g, 2.18 mmol) in 50 mL MeOH was added 20% Pd/C (0.20 g), and the mixture was hydrogenated in a Parr shaker at 48 psi for 23 h. The mixture was filtered and concentrated. To the crude aminoester in 10 mL CH_2Cl_2 was added 1.0 mL trifluoroacetic acid, and the solution stirred at ambient temperature overnight. The mixture was concentrated, and the residue dissolved in the minimum amount of H_2O, and loaded onto DOWEX-50WX8-100 ion exchange resin. The column was eluted with H_2O until neutral to litmus, then continued with 5% aq. NH_4OH (100 mL). The alkaline fractions were concentrated to provide 0.25 g (66%, two steps) of the amino acid as an off-white solid. ^1H NMR (CD3OD) δ 3.41 (m, 1H), 2.36 (dd, J=5.1, 16.6 Hz, 1H), 2.25 (dd, J=8.1, 16.6 Hz, 1H), 1.42 (m, 2H), 1.24 (m, 1H), 1.12 (m, 2H), 1.00 (m, 1H), 0.73 (d, J=6.4 Hz, 3H), 0.68 (t, J=6.8 Hz, 3H). LRMS: m/z 172.1 (M−1).

EXAMPLE 9

2-Aminomethyl-8-methyl-nonanoic acid

[0282] A procedure similar to that of 2-Aminomethyl-4,4,8-trimethyl-nonanoic acid was utilized to prepare 2-Aminomethyl-8-methyl-nonanoic acid from 6-methyl-1-heptanol m/z 202.1 (M+).

2-Aminomethyl-4,8-dimethyl-nonanoic acid

[0283] (R)-2,6-dimethyl heptan-1-ol: Magnesium turnings (2.04 g, 84 mmol) and a crystal of iodine were suspended in 5 mL THF for the addition of 1-bromo-3-methyl butane (0.3 mL, neat). The mixture was heated to start the Grignard formation. The remaining 1-bromo-3-methyl butane (8.63 mL, 72 mmol) was diluted in THF (60 mL) and added dropwise. The mixture was stirred at ambient temperature for 2 hours and cooled to −5° C. A solution of copper chloride (1.21 g, 9 mmol) and LiCl (0.76 g, 18 mmol) in THF (50 mL) was added dropwise keeping the temperature below 0° C. The resulting mixture was stirred for 20 min, and (R)-3-bromo-2-methylpropanol in THF (20 mL) was added dropwise while keeping the temperature below 0° C. The mixture was allowed to slowly reach ambient temperature overnight. The reaction mixture was quenched with ammonium hydroxide and water. The mixture was diluted with EtOAc and extracted with 3×20 mL EtOAc. The organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residual oil was purified via silica gel chromatography (90/10 Hexane/EtOAc) to give 2.67 g (R)-2,6-dimethyl heptan-1-ol.

[0284] (R)-1-iodo-2,6-dimethyl heptane: To a mixture of supported triphenyl phosphine (6.55 g, 19.67 mmol) in CH_2Cl_2 at 0° C. was added iodine (4.99 g, 19.67 mmol) and imidazole (1.33 g, 19.67 mmol). The mixture was warmed to ambient temperature, stirred for 1 h and cooled to 0° C. for the dropwise addition of (R)-2,6-dimethyl heptan-1-ol in CH_2Cl_2 (5 mL). The mixture was allowed to reach ambient temperature and stirred for 1 h, at which time it was filtered through a pad of celite and the solids were washed with CH_2Cl_2. The filtrated was concentrated, and the crude product was purified via silica gel chromatography to give (R)-1-iodo-2,6-dimethyl heptane (2.44 g).

[0285] (4R)-4,8-dimethyl nonanoic acid t-butyl ester: To diisopropyl amine (0.827 mL, 5.9 mmol) in THF (8 mL) at −78° C. was added nBuLi (2.65 mL of a 2.6 M solution in pentane). The solution was stirred for 30 min at −78° C., followed by the addition of t-butyl acetate (0.8 mL, 5.9 mmol). The mixture was stirred at −78° C. for 2 h, and then (R)-1-iodo-2,6-dimethyl heptane (0.3 g, 1.18 mmol) and HMPA (1.5 mL) in THF (1 mL) was added. The reaction was stirred at −78° C. and allowed to slowly reach ambient temperature overnight, then heated at 35° C. to drive the reaction to completion. The reaction was quenched by the addition of ammonium chloride (saturated aqueous solution), and the mixture was extracted with EtOAc (2×10 mL). The organics were combined, washed with water, dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography (98/2 hexane/EtOAc) provided 0.25 g of (4R)-4,8-dimethyl nonanoic acid t-butyl ester.

[0286] (4R)-4,8-dimethyl nonanoic acid: (4R)-4,8-dimethyl nonanoic acid t-butyl ester in 25 mL CH_2Cl_2 at 0° C. was treated with TFA (6 mL). The mixture was allowed to reach ambient temperature and stir overnight. The solvent was removed by rotary evaporation, and the mixture was purified by silica gel chromatography (95/5 hexane/EtOAc) to give 0.962 g (4R)-4,8-dimethyl nonanoic acid. m/z 185 (M−).

[0287] 3-(4R,8-Dimethyl-nonanoyl)-4(S)-methyl-5(R)-phenyl-oxazolidin-2-one: A procedure similar to (4R,5S)-4-Methyl-3-(R)-4-methyl-heptanoyl)-5-oxazolidin-2-one was

utilized to give 3-(4R,8-Dimethyl-nonanoyl)-4(S)-methyl-5(R)-phenyl-oxazolidin-2-one (1.35 g) m/z 346.5 (M+).

[0288] [4R,8-Dimethyl-2R-(4R-methyl-2-oxo-5R-phenyl-oxazolidine-3-carbonyl)-nonyl]-carbamic acid benzyl ester: To a solution of 3-(4(R),8-Dimethyl-nonanoyl)-4(S)-methyl-5(R)-phenyl-oxazolidin-2-one (1.05 g, 3.04 mmol) in CH_2Cl_2 (12 mL) and $TiCl_4$ (3.04 mL of a 1 M solution in CH_2Cl_2) was added diisopropyl ethyl amine (0.55 mL, 3.19 mmol)at −20° C. The resulting dark red solution was stirred at −20° C. for 30 min prior to the addition of a solution of N-methoxymethyl benzyl carbamate (0.652 g, 3.34 mmol) in CH_2Cl_2 (3.5 mL) and $TiCl_4$ (3.34 mL). The mixture was stirred at 0° C. for 4 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The mixture was extracted with CH_2Cl_2 (3×15 mL). The organics were combined and washed with 1 N HCl and neutralized with NaOH, followed by washing with brine. The organics were dried ($MgSO_4$), filtered, concentrated and purified by silica gel chromatography (95/5 hexane/EtOAc) to give 0.555 g [4R,8-Dimethyl-2R-(4R-methyl-2-oxo-5R-phenyl-oxazolidine-3-carbonyl)-nonyl]-carbamic acid benzyl ester.

[0289] 2(R)-(Benzyloxycarbonylamino-methyl)-4(R),8-dimethyl-nonanoic acid; A procedure similar to that of (S)-2-((R)-2-Methyl=pentyl)succinic acid t-butyl ester was utilized to provide 0.198 g 2(R)-(Benzyloxycarbonylamino-methyl)-4(R),8-dimethyl-nonanoic acid.

[0290] 2-aminomethyl-4,8-dimethyl nonanoic acid: 2(R)-(Benzyloxycarbonylamino-methyl)-4(R),8-dimethyl-nonanoic acid (0.148 g, 0.566 mmol) was treated with hydrogen in the presence of 20% pd/C to give 0.082 g of 2-aminomethyl-4,8-dimethyl nonanoic acid after filtration and purification via silica gel chromatography (85/15 CH_2Cl_2/MeOH). m/z 216.3 (M+).

EXAMPLE 10

2-Aminomethyl-4,4,8-trimethyl-nonanoic acid

[0291] 2,2,6-Trimethyl-heptanoic acid methyl ester: To diisopropyl amine (1.54 mL, 11.03 mmol) in THF (22 mL) at −78° C. was added nBuLi (6.89 mL of a 1.6 M solution in hexane). The solution was stirred for 30 min at −78° C., followed by the addition of methyl isobutyrate (0.97 mL, 8.48 mmol). The mixture was stirred at −78° C. for 2 h, and then 1-iodo-4-methyl pentane (1.8 g, 8.48 mmol) and DMPU (0.55 mL, 4.24 mmol) in THF (6 mL) was added. The reaction was stirred at −78° C. and allowed to slowly reach ambient temperature over 16 h. The reaction was quenched by the addition of ammonium chloride (saturated aqueous solution), and the mixture was extracted with EtOAc (2×10 mL). The organics were combined, washed with water, dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography (99/1 hexane/EtOAc) provided 1.57 g of 2,2,6-Trimethyl-heptanoic acid methyl ester.

[0292] 2,2,6-Trimethyl-heptan-1-ol: 2,2,6-Trimethyl-heptanoic acid methyl ester (1.97 g, 10.6 mmol) was taken up in toluene (65 mL) and cooled to −78° C. DiBALH (12.7 mL of a 1 N solution in toluene) was added dropwise. After 45 min, 1.5 mL DiBALH was added. After 2 h, the reaction was quenched by the addition of 15 mL MeOH at −78° C. The mixture was warmed to ambient temperature, and then cooled again to −78° C. for the addition of 10 mL 1 N HCl. The mixture was extracted with EtOAc (3×15 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residual oil was purified via silica gel chromatography (95/5 Hexane/EtOAc) to give 2,2,6-Trimethyl-heptan-1-ol (0.88 g). m/z 159 (M+).

[0293] 2,2,6-Trimethyl-heptanal: Pyridinium chlorochromate (PCC, 4.17 g, 19.4 mmol) was combined with neutral alumina (14.6 g) in CH_2Cl_2 and stirred at ambient temperature for 15 min. The alcohol was diluted in CH_2Cl_2, and the mixture was stirred at ambient temperature for 2 h. The solution was filtered through a pad of silica, and the solids were washed with CH_2Cl_2. The filtrate was evaporated to give 1.05 g m/z 157 (M+).2,2,6-Trimethyl-heptanal which was carried on without further purification.

[0294] 2-Cyano-4,4,8-trimethyl-non-2-enoic acid benzyl ester: To a mixture of 2,2,6-Trimethyl-heptanal (1.05 g, 6.73 mmol), piperidine (0.19 mL, 2.01 mmol) and benzyl cyanoacetate (1.29 g, 7.4 mmol) in toluene (50 mL) was added glacial acetic acid (0.72 g, 12.1 mmol). The flask was fitted with a Dean-Stark trap, and the mixture was heated at reflux for 18. The mixture was cooled, treated with dilute HCl, and the layers were separated. The organics were washed with a saturated sodium bicarbonate solution followed by brine, and dried ($MgSO_4$), filtered and concentrated. The residual oil was purified by silica gel chromatography (98/2 hexane/EtOAc) to give 1.3 g of 2-Cyano-4,4,8-trimethyl-non-2-enoic acid benzyl ester m/z 314 (M+).

[0295] 2-aminomethyl-4,4,8-trimethyl-nonanoic acid: 2-Cyano-4,4,8-trimethyl-non-2-enoic acid benzyl ester (1.3 g, 4.14 mmol) in THF (50 mL) was treated with hydrogen in the presence of 20% Pd/C to give a mixture of the cyano acid and the cyano methyl ester. The mixture was purified by silica gel chromatography to give 278 mg of 80105x41-1-2. The acid was then treated with hydrogen in the presence of Raney Ni in MeOH/NH4OH to give 0.16 g of 2-aminomethyl-4,4,8-trimethyl-nonanoic acid. m/z 230.3 (M+).

EXAMPLE 11

2-Aminomethyl-4-ethyl-octanoic acid

[0296] A procedure similar to that of 2-Aminomethyl-4,4,8-trimethyl-nonanoic acid was utilized to prepare 2-Aminomethyl-4-ethyl-octanoic acid from 2-ethylhexanal. m/z 202.1 (M+).

EXAMPLE 12

2-Aminomethyl-4-ethyl-8-methyl-nonanoic acid

[0297] A procedure similar to that of 2-Aminomethyl-4,4,8-trimethyl-nonanoic acid was utilized to prepare 2-Aminomethyl-8-methyl-nonanoic acid from 2,6-di-t-butyl-4-methylphenyl cyclopropylcarboxylate. m/z 230.2 (M+).

EXAMPLE 13

3-Amino-2-[1-(4-methyl-pentyl)-cyclopropylmethyl]-propionic acid

[0298] A procedure similar to that of 2-Aminomethyl-4,4,8-trimethyl-nonanoic acid was utilized to prepare 2-Aminomethyl-8-methyl-nonanoic acid from 2,6-di-t-butyl-4-methylphenyl cyclopropylcarboxylate. m/z 228.2 (M+).

EXAMPLE 14

2-Aminomethyl-4-ethyl-hexanoic acid

[0299] A procedure similar to 2-aminomethyl-4,8-dimethyl-nonanoic acid was used to prepare 2-aminomethyl-4-ethyl-hexanoic acid from 4-ethyl hexanoic acid. m/z 174.1.

EXAMPLE 15

3(S)-Amino-3,5-dimethyl-heptanoic acid

[0300] 2-Methyl-propane-2(S)-sulfinic acid (1,3-dimethyl-pentylidene)-amide: A solution of (S)-(−)-2-methyl-2-propanesulfonamide (500 mg, 4.1 mmol), 4-methyl-2-hexanone (470 mg, 4.1 mmol), and Titanium(IV) ethoxide (1.7 mL, 8.3 mmol) was heated at reflux for 18 h. The reaction mixture was poured into 20 mL brine with rapid stirring. The resulting solution was filtered through celite, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The resultant oil was purified by silica gel chromatography (25% EtOAc in hexane) to give 575 mg of 2-Methyl-propane-2(S)-sulfinic acid (1,3-dimethyl-pentylidene)-amide as a yellow oil.

[0301] 3,5-Dimethyl-3-(2-methyl-propane-2(S)-sulfinylamino)-heptanoic acid methyl ester: To a −78° C. solution of lithium bis(trimethylsilyl)amide (5.1 ml of a 1 M solution in THF) in THF (6 mL) was added methyl acetate ((0.41 mL, 5.1 mmol) dropwise. After stirring for 20 min, a solution of chlorotitanium triisopropoxide (2.5 ml, 10 mmol) in THF (3 mL) was added dropwise. After 1 hour, 2-Methyl-propane-2(S)-sulfinic acid (1,3-dimethyl-pentylidene)-amide (560 mg, 2.6 mmol) in THF (3 mL) was added dropwise at −78° C. The reaction was stirred at −78° C. for 5 h, and then quenched by the addition of 10 mL ammonium chloride solution and warmed to room temperature. The mixture was diluted with 10 mL water, and filtered. The aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resultant oil was purified by silica gel chromatography (30% EtOAc in hexane) to give 360 mg of 3,5-Dimethyl-3-(2-methyl-propane-2(S)-sulfinylamino)-heptanoic acid methyl ester.

[0302] 3(S)-Amino-3,5-dimethyl-heptanoicacid: 3,5-Dimethyl-3-(2-methyl-propane-2(S)-sulfinylamino)-heptanoic acid methyl ester (360 mg, 1.2 mmol) was dissolved in 6 N HCl (2 mL) and dioxane (2mL) and heated at 100 C for 6 h. The mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (15 mL). The organics were purified by ion exchange chromatography to give 3(S)-Amino-3,5-dimethyl-heptanoic acid (270 mg) and then repurification by silica gel chromatography (70:25:5 CH_2Cl_2/MeOH/NH_4OH) to give 203 mg of 3(S)-Amino-3,5-dimethyl-heptano acid as a white solid. m/z 174 ($C_9H_{19}NO_2$+H).

EXAMPLE 16

3(S)-Amino-3,5-dimethyl-nonanoic acid

[0303] A procedure similar to that of 3(S)-Amino-3,5-dimethyl-heptanoic acid was used to prepare 3(S)-Amino-3,5-dimethyl-nonanoic acid. m/z 202.1 ($C_{11}H_{23}NO_2$+H).

Pharmaceutical Composition Examples

[0304] In the following Examples, the term 'active compound' or 'active ingredient' refers to a suitable combination or individual element of an alpha-2-delta ligand and a PDEV inhibitor and/or a pharmaceutically acceptable salt or solvate, according to the present invention.

(i) Tablet Compositions

[0305] The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Sodium Starch Glycollate	20	12
(d)	Povidone B.P.	15	9
(e)	Magnesium Stearate	5	3
		500	300

[0306]

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose	150	150
(c)	Avicel PH 101	60	26
(d)	Sodium Starch Glycollate	20	12
(e)	Povidone B.P.	15	9
(f)	Magnesium Stearate	5	3
		500	300

[0307]

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

[0308] The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in formulation E is of the direct compression type.

Composition D	
	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

[0309]

Composition E	
	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

[0310]

Composition F (Controlled release composition)		
		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium Stearate	7
		700

[0311] The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-Coated Tablet)

[0312] Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25 mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-Coated Controlled Release Tablet)

[0313] Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50 mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule Compositions

Composition A

[0314] Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B		
		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

[0315]

Composition C		
		mg/capsule
(a)	Active ingredient	250
(b)	Macrogol 4000 BP	350
		600

[0316] Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D	
	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

[0317] Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)		
		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Ethyl Cellulose	13
		513

[0318] The controlled release capsule formulation can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)		
		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Cellulose Acetate Phthalate	50
(e)	Diethyl Phthalat	5
		555

[0319] The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-Coated Controlled Release Capsule)

[0320] Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50 mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) or a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition	
Active ingredient	0.200 g
Sterile, pyrogen-free phosphate buffer (pH 9.0) to	10 ml

[0321] The active ingredient is dissolved in most of the phosphate buffer at 35-40° C., then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition	
Active ingredient	0.20 g
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for Injection q.s. to	3.00 ml

[0322] The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition	
Active ingredient	0.25 g
Sorbitol Solution	1.50 g
Glycerol	1.00 g
Sodium Benzoate	0.005 g
Flavour	0.0125 ml
Purified Water q.s. to	5.0 ml

[0323] The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition	
	mg/suppository
Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770
	2020

[0324] One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45° C. maximum. The active ingredient is sifted through a 200 lm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45° C., the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250 lm stainless steel screen and, with continuous stirring, allowed to cool to 40° C. At a temperature of 38-40° C., 2.02 g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition	
	mg/pessary
Active ingredient (63l m)	250
Anhydrous Dextrose	380

-continued

(vii) Pessary composition	
	mg/pessary
Potato Starch	363
Magnesium Stearate	7
	1000

[0325] The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

(viii) Transdermal composition	
Active ingredient	200 mg
Alcohol USP	0.1 ml
Hydroxyethyl cellulose	

[0326] The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm^2.

1. A combination comprising a synergistic ratio of an alpha-2-delta ligand and a PDEV inhibitor, or a pharmaceutically acceptable salt or solvate of any thereof.

2. A combination according to claim 1, wherein the alpha-2-delta ligand is selected from gabapentin, pregabalin, [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4] oxadiazol-5-one and C-[1-(1-H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)(3-aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-Aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-Amino-5-methyl-octanoic acid, or a pharmaceutically acceptable salt or solvate thereof.

3. A combination according to claim 2 where the alpha-2-delta ligand is gabapentin, or a pharmaceutically acceptable salt or solvate thereof.

4. A combination according to claim 2 where the alpha-2-delta ligand is pregabalin, or a pharmaceutically acceptable salt or solvate thereof.

5. A combination according to claim 1 wherein the PDEV inhibitor is selected from:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil);

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (tadalafil, IC-351);

2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil);

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine;

or a pharmaceutically acceptable salt or solvate thereof.

6. A combination according to claim 1 wherein the PDEV inhibitor is sildenafil, or a pharmaceutically acceptable salt or solvate thereof.

7. A combination according to claim 1 wherein the PDEV inhibitor is vardenafil, or a pharmaceutically acceptable salt or solvate thereof.

8. A combination according to claim 1 wherein the PDEV inhibitor is tadalafil, or a pharmaceutically acceptable salt or solvate thereof.

9. A method for the treatment of pain in a mammal comprising administering to a mammal a combination according to claim 1.

10. A method according to claim 9, wherein the pain is neuropathic pain.

11. A combination comprising an alpha-2-delta ligand, excluding gabapentin, pregabalin and compounds of formula (i)-(xxv) of PCT/IB02/01146 and a PDEV inhibitor.

13. A pharmaceutical composition comprising a therapeutically effective amount of a combination as claimed in claim 1 together with a pharmaceutically suitable excipient or carrier.

14. A synergistic combination for human administration comprising an alpha-2-delta ligand and a PDEV inhibitor, or pharmaceutically acceptable salts or solvates thereof, in a w/w combination range which corresponds to a synergistic combination range of the order of 1:1 to 10:1 parts by weight in the rat model of CCI induced static allodynia.

15. A synergistic combination for administration to humans comprising an alpha-2-delta ligand and a PDEV inhibitor, or pharmaceutically acceptable salts or solvates thereof, according to claim 1, where the dose ranges of the alpha-2-delta ligand and PDEV inhibitor correspond to a synergistic dose range of 1-10 mg/kg and 0.1-1 mg/kg respectively, in the rat model of CCI induced static allodynia.

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5 Comprobante de pago No. 08 - 31.249 (Oposición) Fecha Abril 16 de 2008
08 - 31.252 (Prórroga) Fecha Abril 16 de 2008

6 **Anexos:**

- [x] Comprobante de pago de la tasa
- [x] Poderes, si fuere el caso
- [ ] Pruebas de los fundamentos de la oposición
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso
- [x] Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- [x] Copia de la oposición para el traslado al solicitante.

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