352

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**F. HOFFMANN-LA ROCHE AG**.-Solicitud de Patente de Invención en Fase Nacional PCT para **"NUEVOS DERIVADOS DE DICARBOXAMIDA"**.-Clase **C07D 213/64**.-Expediente número **07-055.084**.-

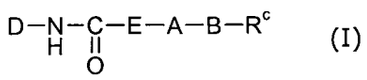
1. Me refiero a mi memorial de 26 de Septiembre de 2007.

2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **587** de 18 de Enero de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.

3. Por otro lado, atentamente me permito manifestar a usted que en el extracto de la solicitud arriba nombrada, publicado en la Gaceta de la Propiedad Industrial número **587** de 18 de Enero de 2007, página 310, el nombre del inventor GROEBKE **ZBINDEN** aparece publicado en forma equivocada. Adicionalmente, la reivindicación número **1** aparece publicada en forma equivocada, la reivindicación número 1 correcta es como sigue a continuación:

Reivindicación número 1.-

Compuestos de la fórmula (I)



(I)

en la que

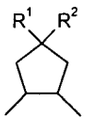
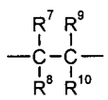
A es –CONH- o -NHCO-;

B es fenilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heterociclilo opcionalmente sustituido;

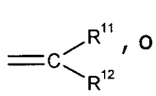
R^c es arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heterociclilo opcionalmente sustituido, uno o dos átomos de carbono de dicho anillo

arilo, heteroarilo o heterociclilo pueden estar opcionalmente sustituido por un grupo carbonilo;

D es arilo opcionalmente sustituido por uno, dos o tres átomos de halógeno elegidos con independencia entre cloro, flúor y bromo o heteroarilo opcionalmente sustituido por uno, dos o tres átomos de halógeno elegidos con independencia entre cloro, flúor y bromo;

E es E-1:  , E-2:  o E-3:  ;

R^1 y R^2 con independencia entre sí son hidrógeno, halógeno, alquilo C_{1-6}, cicloalquilo C_{3-7}, cicloalquil $_{3-7}$-alquilo C_{1-6}, amino, amino monosustituido, amino disustituido, hidroxi, alcoxi C_{1-6}, amino monosustituido-alquilo C_{1-6}, amino disustituido-alquilo C_{1-6}, hidroxil-alquilo C_{1-6} o

R^1 y R^2 juntos forman =O o  , o

R^1 y R^2 están unidos entre sí para formar heterociclilo opcionalmente sustituido, junto con el átomo de carbono al que R^1 y R^2 están unidos;

R^3 y R^4 con independencia entre sí son hidrógeno, alquilo C_{1-6}, carboxilo, alcoxicarbonilo C_{1-6}, carbamoílo, amino mono- o disustituido-carbonilo, heterociclilocarbonilo opcionalmente sustituido, heteroarilocarbonilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, hidroxil-alquilo C_{1-6}, halo-alquilo C_{1-6}, ciano-alquilo C_{1-6}, alcoxi C_{1-6}-alquilo C_{1-6}, amino-alquilo C_{1-6}, amino mono- o disustituido-alquilo C_{1-6}, arilo alquilo C_{1-6} opcionalmente sustituido, heterociclilo alquilo C_{1-6} opcionalmente sustituido, heteroarilo alquilo C_{1-6} opcionalmente sustituido, ariloalcoxi C_{1-6} alquilo C_{1-6} opcionalmente sustituido, heteroariloalcoxi C_{1-6} alquilo C_{1-6} opcionalmente sustituido, heterociclilo alcoxi C_{1-6}-alquilo C_{1-6} opcionalmente sustituido o

R^3 y R^4 están unidos entre sí para formar cicloalquilo C_{3-7}, junto con el átomo de carbono al que R^3 y R^4 están unidos;

R^5 y R^6 con independencia entre sí son hidrógeno, alquilo C_{1-6}, ciano, alcoxicarbonilo C_{1-6}, alqueniloxicarbonilo C_{2-6}, alquiniloxicarbonilo C_{2-6}, hidroxil-alquilo C_{1-6},

anillo son C, y uno o dos átomos de carbono del anillo pueden reemplazarse por un grupo carbonilo;

el término "heterociclilo opcionalmente sustituido" significa un grupo heterociclilo, que está opcionalmente sustituido con independencia entre sí por uno, dos o tres sustituyentes elegidos entre el grupo formado por halógeno, hidroxi, alquilo C_{1-6}, halo-alquilo C_{1-6}, alcoxi C_{1-6}, alquilsulfonilo C_{1-6}, alquilsulfinilo C_{1-6}, alquiltio C_{1-6}, amino, amino-alquilo C_{1-6}, amino mono- o disustituido-alquilo C_{1-6}, nitro, ciano, acilo, carbamoílo, amino mono- o disustituido, aminocarbonilo, amino mono- o disustituido-carbonilo, aminocarbonil-alcoxi C_{1-6}, amino mono- o disustituido-carbonil-alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, carboxilo, alcoxicarbonilo C_{1-6}, aril-alcoxi C_{1-6}, heteroaril-alcoxi C_{1-6}, heterociclil-alcoxi C_{1-6}, alcoxicarbonilo C_{1-6}-alcoxi C_{1-6}, carbamoil-alcoxi C_{1-6} y carboxil-alcoxi C_{1-6};

el término "heteroarilo" significa un resto monocíclico o bicíclico de 5 a 12 átomos en el anillo que tiene por lo menos un anillo aromático que contiene uno, dos o tres heteroátomos en el anillo elegidos entre N, O y S, los demás átomos del anillo son C, dando por supuesto que el punto de unión del heteroarilo radical estará situado en un anillo aromático, y uno o dos átomos de carbono del anillo pueden reemplazarse por un grupo carbonilo;

el término "heteroarilo opcionalmente sustituido" significa un grupo heteroarilo, que está opcionalmente sustituido con independencia entre sí por uno, dos o tres sustituyentes elegidos entre el grupo formado por halógeno, hidroxi, alquilo C_{1-6}, halo-alquilo C_{1-6}, alcoxi C_{1-6}, alquilsulfonilo C_{1-6}, alquilsulfinilo C_{1-6}, alquiltio C_{1-6}, amino, amino-alquilo C_{1-6}, amino mono- o disustituido-alquilo C_{1-6}, nitro, ciano, acilo, carbamoílo, amino mono- o disustituido, aminocarbonilo, amino mono- o disustituido-carbonilo, aminocarbonil-alcoxi C_{1-6}, amino mono- o disustituido-carbonil-alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, carboxilo, alcoxicarbonilo C_{1-6}, aril-alcoxi C_{1-6}, heteroaril-alcoxi C_{1-6}, heterociclil-alcoxi C_{1-6}, alcoxicarbonilo C_{1-6}-alcoxi C_{1-6}, carbamoil-alcoxi C_{1-6} y carboxil-alcoxi C_{1-6};

el término "amino monosustituido" y "amino disustituido" significan –NHR y –NRR' respectivamente, en los que R y R' se eligen con independencia entre sí entre el grupo formado por hidroxi, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, alcoxi C_{1-6}-alquilo C_{1-6}, carbamoílo alquilo C_{1-6}, halo-alquilo C_{1-6}, cicloalquilo C_{3-7}, cicloalquil $_{3-7}$-alquilo C_{1-6}, alcoxi C_{1-6}, alquilsulfonilo C_{1-6}, alquilsulfinilo C_{1-6}, alquiltio C_{1-6}, amino mono- o disustituido por

alquilo C_{1-6}-sulfonilo, amino mono- o disustituido por alquilo C_{1-6}-sulfinilo, amino mono- o disustituido por alquilo C_{1-6}-tio, amino mono- o disustituido por alquilo C_{1-6}-alquilo C_{1-6}, amino mono- o disustituido por alquilo C_{1-6}-carbonil-alquilo C_{1-6}, acilo, haloalquil C_{1-6}-carbonilo y alcoxi C_{1-6}-carbonilo;

el término "acilo" significa –C(=O)R, en el que R es H o alquilo C_{1-6};

el término "haloalquilo C_{1-6}" significa alquilo C_{1-6} sustituido por uno o varios átomos de halógeno iguales o diferentes elegidos con independencia entre sí entre el grupo formado por cloro, flúor y bromo.

4. En vista de lo anterior, muy comedidamente solicito a usted que las aclaraciones correspondientes sean incluidas en la Fe de Erratas de la próxima Gaceta de la Propiedad Industrial.

5. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo II.

6. Anexo me permito presentar recibo número 08-51.936, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

7. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

357

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-055084- -00003-0000

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Tra. 11 PATENTEIYII Eve. 379 FASENACIONALII
Act. 538 PETICION Folios: 5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 51,936
FECHA : JULIO 1 DE 2008

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

SITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	1859843	01/07/2008	7,765,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
		TOTAL : $	210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-55084

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

D1

359

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

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International Bureau

(43) International Publication Date
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PCT

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WO 01/64642 A2

(51) International Patent Classification[7]: C07D 213/75, 317/44, 213/80, 213/79, C07C 311/46, C07D 401/12, 233/26, 295/18, C07C 257/18, C07D 203/18, 205/04, 409/14, 409/12, 401/14, 231/40, 403/12, 217/22, 333/38, A61K 31/18, 31/44, A61P 7/02

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(22) International Filing Date: 28 February 2001 (28.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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09/663,420	15 September 2000 (15.09.2000)	US

(71) Applicant *(for all designated States except US)*: **COR THERAPEUTICS, INC.** [US/US]; 256 E. Grand Avenue, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHU, Bing-Yan** [CA/US]; 3325 Adelaide Way, Belmont, CA 94002-1223 (US). **ZHANG, Penglie** [CN/US]; 251 Winchester Court, Foster City, CA 94404 (US). **WANG, Lingyan** [CN/US]; 25 Hickory Place #C-5, Chatham, NJ 07928 (US). **HUANG, Wenrong** [CN/US]; 7723 Huntridge Lane, Cupertino, CA 95014 (US). **GOLDMAN, Erick** [US/US]; 1577 Pershing Drive #C, San Francisco, CA 94129 (US). **LI, Wenhao** [CN/US]; P.O. Box 1993, South San Fransicso, CA 94083 (US). **ZUCKETT, Jingmei** [CN/US]; 5615 West Acoma Drive #102, Glendale, AZ 85306 (US). **SONG, Yonghong** [CA/US]; 1144 Nimitz Lane, Foster City, CA 94404 (US). **SCARBOROUGH, Robert** [US/US]; 22 Greenbrier Court, Half Moon Bay, CA 94019 (US).

(74) Agent: **LEE, Christine, S.**; Morgan, Lewis & Bockius LLP, 1800 M Street, N.W., Washington, DC 20036-5869 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:

— *without international search report and to be republished upon receipt of that 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 01/64642 A2

(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

(57) Abstract: Novel benzamide compounds including their pharmaceutically acceptable isomers, salts,hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa aredescribed. Compositions containing such compounds are also described. The compounds andcompositions are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

$C(=O)$-$N(R^{2e}, R^{3e})$; -O-C_{1-4}-alkyl-$C(=O)$-O-R^{2e}; -C_{0-2}-alkyl-$N(R^{2e})$-$C(=O)$-R^{3e}; -C_{0-2}-alkyl-$N(-R^{2e})$-SO_2-R^{3e}; -CH_2-$N(R^{2e})$-$C(=O)$-R^{3e} ;-CH_2-$N(R^{2e})$-SO_2-R^{3e}; -$(CH_2)_{0-6}$-$NR^{2e}R^{3e}$; -$C(=O)$-$N(R^{2e},R^{3e})$; -$N(-(CH_2)_{1-6}$-$OR^{2e})_2$; -$N(R^{10})$-$(CH_2)_{1-6}$-OR^{2e}; -$N(R^{10})$-$C(=O)$-R^{2e}; -$N(R^{10})$-SO_2-R^{2e}; -$C(=N(R^{10}))$-$N(R^{2e},R^{3e})$; and a -$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-2}-alkyl-O-R^{1g}; -C_{0-2}-alkyl-$N(-R^{1g}, -R^{2g})$;-C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3c} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -$C(=O)$-$N(R^{3g})R^{4g}$; -$C(=O)$-OR^{3g}; -NO_2; -$(CH_2)_p$-$NR^{3g}R^{4g}$; -$SO_2NR^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_pOR^{3g}$;

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

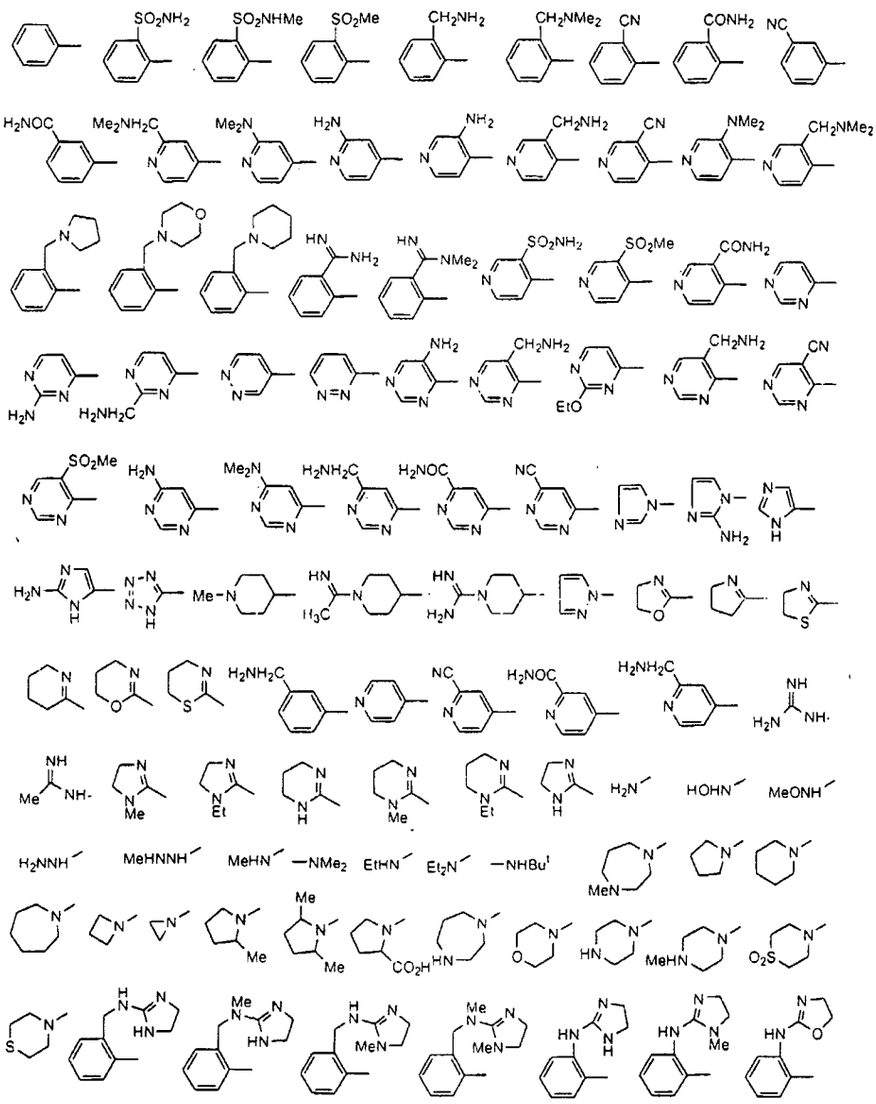
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of formula I are compounds of formula (Ic):

A-Q-D-E-G-J-X (Ic)

where:

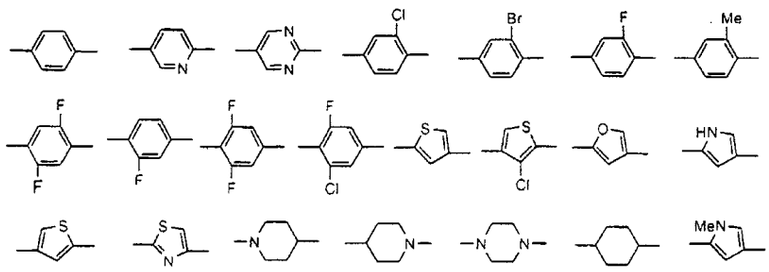
A is a member selected from the group consisting of:



Q is a member selected from the group consisting of:

a direct link, -C(=O)-, -NH-, -NMe-, -NHCH$_2$-, -NMeCH$_2$-, -C(=NH)-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

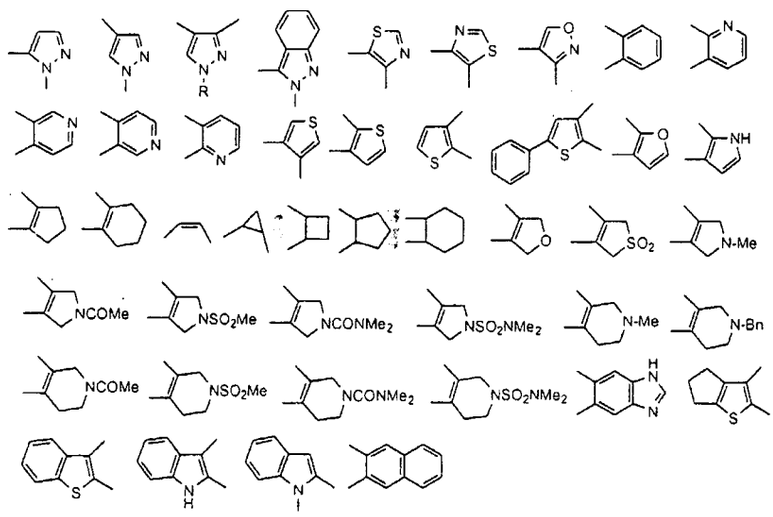


;

E is a member selected from the group consisting of:

a direct link, $-CH_2NH-$, $-C(=O)-NH-$, $-NH-C(=O)-$;

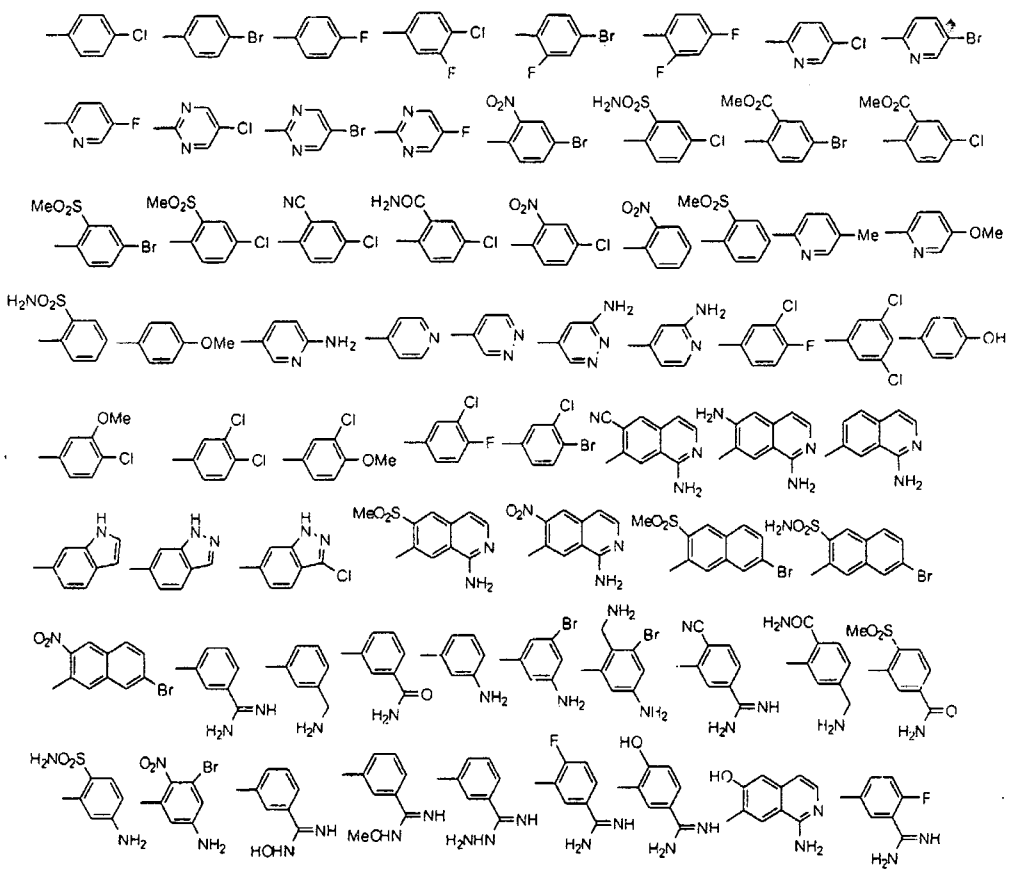
G is a member selected from the group consisting of:



;

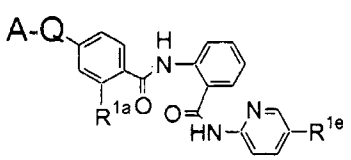
G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-NMe_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, $-C(=O)-OMe$, $-CO_2H$, $-CONH_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHC(=O)Me$, $-C(=O)N(-Me)_2$, $-CH_2NH_2$, $-CH_2N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$ and $-OCH_2C(=O)N(-Me)_2$.



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment of the invention are compounds of the following formula (II):



(II)

where:

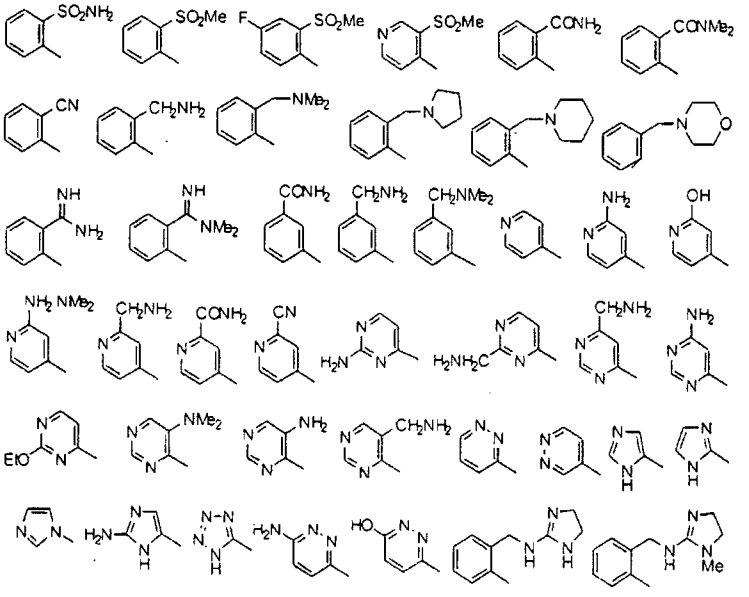
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

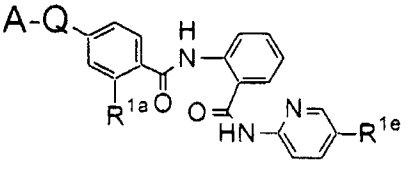
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment the invention are compounds of formula (III):



(III)

where:

R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

D2.

363

US 20030162787A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0162787 A1**

Bigge et al. (43) **Pub. Date: Aug. 28, 2003**

(54) **INHIBITORS OF FACTOR XA AND OTHER SERINE PROTEASES INVOLVED IN THE COAGULATION CASCADE**

(76) Inventors: **Christopher Franklin Bigge**, Ann Arbor, MI (US); **Agustin Casimiro-Garcia**, Ann Arbor, MI (US); **Danette Andrea Dudley**, Ann Arbor, MI (US); **Jeremy John Edmunds**, Ypsilanti, MI (US); **Kevin James Filipski**, Canton, MI (US); **Jeffrey Thomas Kohrt**, Ann Arbor, MI (US); **Chad Alan Van Huis**, Plymouth, MI (US)

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WARNER-LAMBERT COMPANY
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(21) Appl. No.: **10/278,643**

(22) Filed: **Oct. 23, 2002**

Related U.S. Application Data

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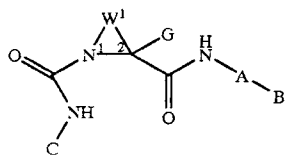
(57) **ABSTRACT**

The present invention provides compounds of Formula (I):

I



wherein A, B, C, G, and W^1 have any of the values defined in the specification, and pharmaceutically acceptable salt thereof, that are useful to treat thrombotic disorders. Also disclosed are pharmaceutical compositions comprising one or more compounds of Formula I, processes for preparing compounds of Formula I, and intermediates useful for preparing compounds of Formula I.

[0010] (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_7)cycloalkenyl, (C_4-C_7)heterocycloalkenyl, aryl, or heteroaryl, any of which may be optionally substituted by halo, (C_1-C_6)alkyl, or halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, —CN, haloalkyl, amino, alkylamino, amidino, amido, or sulfonamido;

[0011] C is phenyl or heteroaryl, wherein phenyl or heteroaryl is optionally substituted with one or more substituents selected from halogen, hydroxy, —CO_2R^2, —COR^2, —$CONR^2R^{2'}$, alkoxy, alkyl, —CN, haloalkyl, amino, alkylamino, amidino, amido, or sulfonamido;

[0012] G is H, halo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl,

[0013] —CH_2O—(C_1-C_6)alkyl, —CH_2—CO_2(C_1-C_6)alkyl, —CH_2—NR2R2', or —CH_2—CONH(C_1-C_6)alkyl;

[0014] W^1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain or hydrocarbon-heteroatom chain having from 2 to 6 atoms, wherein W^1 connects the nitrogen atom at position 1 to the carbon atom at position 2 to form a four to eight membered ring;

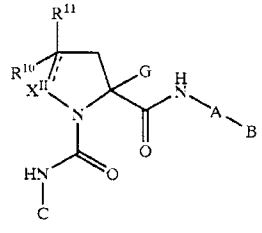
[0015] R^1 is (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_7)cycloalkenyl, (C_4-C_7)heterocycloalkenyl, aryl, monocyclic heteroaryl, or —NR^3R^4;

[0016] R^2 and $R^{2'}$ are each independently H or (C_1-C_6)alkyl; and

[0017] R^3 and R^4 are each independently H, (C_1-C_6)alkyl, aralkyl, aryl, monocyclic heteroaryl, alkoxycarbonyl, aralkoxycarbonyl, —SO_2alkyl, or joined together to form a saturated or unsaturated 3 to 7 membered ring.

[0018] The invention is also directed to a compound of formula II:

II



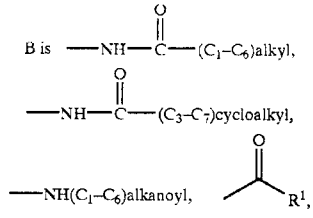
[0019] or a pharmaceutically acceptable salt thereof wherein

[0020] "—" is a bond or is absent;

[0021] X^{II} is CH_2, CH, NH or N;

[0022] R^{10} and R^{11} are each independently H, —OH, halo, alkyl, haloalkyl, —NR^8R^9, —OR^2, —CN, —CH_2OH, —CH_2—NR^3R^4, aryl, monocyclic heteroaryl, alkylaryl, —CH=O, —CH_2OR^2, —COR^2, —CO_2R^2, or —$CONR^3R^4$ or are taken together to form =O, =NOR^2, =$C(C_1$-C_6alkyl$)_2$, or =CR^2H, with the proviso that when "—" is a bond, R^{11} is absent, and X^{II} is CH or N, and R^{10} is H, —OH, halo, alkyl, haloalkyl, —NR^8R^9, —OR^2, —CN, —CH_2OH, —CH_2—NR^3R^4, aryl, monocyclic heteroaryl, alkylaryl, —CH=O, —CH_2OR^2, —COR^2, —CO_2R^2, or —$CONR^3R^4$;

[0023] A is aryl and substituted aryl or monocyclic heteroaryl or substituted monocyclic heteroaryl;



[0024] (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_7)cycloalkenyl, (C_4-C_7)heterocycloalkenyl, aryl, or heteroaryl, any of which may be optionally substituted;

[0025] C is phenyl or heteroaryl, wherein phenyl or heteroaryl is optionally substituted with one or more substituents selected from halogen, hydroxy, —CO_2R^2, —COR^2, —$CONR^2R^{2'}$, alkoxy, alkyl, —CN, haloalkyl, amino, alkylamino, amidino, amido, or sulfonamido;

[0026] G is H, halo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl,

[0027] —CH_2O—(C_1-C_6)alkyl, —CH_2-CO_2(C_1-C_6)alkyl, —CH_2—NR^2R^2, or —CH_2—CONH(C_1-C_6)alkyl;or —CH_2—CONH(C_1-C_6)alkyl;

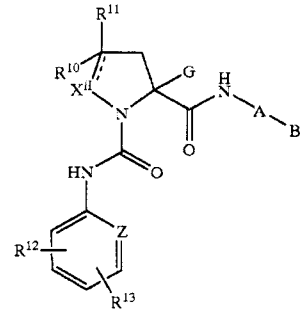
[0028] R^1 is (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_7)cycloalkenyl, (C_4-C_7)heterocycloalkenyl, aryl, monocyclic heteroaryl, or —NR^3R^4;

[0029] R^2 and $R^{2'}$ are each independently H or (C_1-C_6)alkyl; and

[0030] R^3 and R^4 are independently H, (C_1-C_6)alkyl, aralkyl, aryl, monocyclic heteroaryl, alkoxycarbonyl, aralkoxycarbonyl, —SO_2alkyl, or joined together to form a saturated or unsaturated 5 to 7 membered ring.

[0031] The invention is also directed to a compound of Formula III

III



[1100] For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or Formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

[1101] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

[1102] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[1103] Examples of useful dermatological compositions which can be used to deliver the compounds of Formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

[1104] Useful dosages of the compounds of Formula I can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

[1105] Generally, the concentration of the compound(s) of Formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

[1106] The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[1107] The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 2,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 10 mg per kilogram of body weight per day is preferable. However, the specific dosage used can vary. For example, the dosage can depended on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

[1108] Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μM, preferably, about 1 to 50 μM, most preferably, about 0.1 to about 5 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 10-500 mg of the active ingredient. Desirable blood levels may be maintained by multiple oral dosing, or continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

[1109] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

[1110] The following examples illustrate the various embodiments of the present invention. Those skilled in the art will recognize many variations that are within the spirit of the present invention and scope of the claims.

BIOLOGICAL ASSAYS

[1111] The invention compounds have demonstrated factor Xa inhibitory activity in the standard assays commonly employed by those skilled in the art.

[1112] A. Determination of Factor Xa IC_{50}

[1113] The ability of compounds to act as inhibitors of human factor Xa catalytic activity is assessed by determination of that concentration of test substance that inhibits by 50% (IC_{50}) the ability of human factor Xa to cleave the chromogenic substrate S2765 (N-CBz-D-Arg-L-Gly-L-Arg-p-nitroanilide. 2HCl, DiaPharma). The IC_{50} was determined at 3 pM and 30 pM concentrations human factor Xa (Enzyme Research Laboratories). These concentrations were achieved by diluting a 21.087 μM stock solution of factor Xa in the appropriate amount of a buffer comprising 10 μM HEPES, 150 μM NaCl, 0.1% BSA, pH 7.4 (HBSA buffer). Accordingly, 5 μL of the compound to be tested in DMSO (2% final) is added to the factor Xa/buffer solution and incubated for 60 minutes at room temperature.

[1114] The IC_{50} is determined by monitoring the increase in absorbance at 390 nm exicitation, 460 nm emission, with a 455 nm cutoff, in a fluorometric plate reader. Results of the IC_{50} at 3 pM and 30 pM enzyme concentrations are provided in Table 1.

TABLE 1

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
(R)-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]	0.0199	0.0270
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.0355
Pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.2568
Pyrrolidine-1,2-dicarboxylic acid 1-[(2,4-difluoro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		9.1175
Pyrrolidine-1,2-dicarboxylic acid 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide] 1-p-tolylamide	0.3890	

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
Pyrrolidine-1,2-dicarboxylic acid 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide] 1-[(4-methoxy-phenyl)-amide]	0.8730	
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-bromo-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]	0.0333	
Pyrrolidine-1,2-dicarboxylic acid 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide] 1-phenylamide	0.9510	
Pyrrolidine-1,2-dicarboxylic acid 1-[(3,4-difluoro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]	0.6460	
Pyrrolidine-1,2-dicarboxylic acid 1-[(3-fluoro-4-methyl-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]	0.5150	
Pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.0804	
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.0172	
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[5-(2-sulfamoyl-phenyl)-pyridin-2-yl]-amide}	0.0730	
Pyrrolidine-1,2-dicarboxylic acid 2-[(3-chloro-2'-methanesulfonyl-biphenyl-4-yl)-amide] 1-[(5-chloro-pyridin-2-yl)-amide]	0.1010	
Pyrrolidine-1,2-dicarboxylic acid 2-[(3-chloro-2'-methanesulfonyl-biphenyl-4-yl)-amide] 1-[(4-chloro-phenyl)-amide]	0.0166	
Pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[5-(2-sulfamoyl-phenyl)-pyridin-2-yl]-amide}	0.2770	
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.0007	
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-phenyl]-amide}	0.1560	
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.0273	
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfonyl-3-methyl-biphenyl-4-yl)-amide]	0.0591	
(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.000374833	
(2R)-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.007596667	
(2R,4S)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide]-2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.004443333	
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide] 1-p-tolylamide	0.01065	
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide] 1-[(4-fluoro-phenyl)-amide]	0.0028575	
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]	0.0071125	

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfonyl-3-trifluoromethyl-biphenyl-4-yl)-amide]	0.0806	
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0014
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}	0.0025	
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0041
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0149
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0084
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0045
(2R,4R)-4-Propoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0008
(2R,4R)-4-Propoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0020
(2R,4R)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0050
(2R,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0510
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-azetidin-1-yl)-phenyl]-amide}		0.0110
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-azetidin-1-yl)-phenyl]-amide}		0.1223
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-azetidin-1-yl)-phenyl]-amide}		54% at 1 uM
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-pyrrolidin-1-yl)-phenyl]-amide}		0.0040
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-azepan-1-yl)-phenyl]-amide}		0.0294
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-azepan-1-yl)-phenyl]-amide}		0.0041

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.0300
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.0013
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.0004
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		TBD
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-hydroxymethyl-5-oxo-pyrrolidin-1-yl)-phenyl]-amide}		TBD
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2,3-dimethyl-5-oxo-2,5-dihydro-pyrazol-1-yl)-phenyl]-amide}		0.2560
4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2-hydroxymethyl-pyrrolidin-1-yl)-phenyl]-amide}		0.0110
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-pyrrolidin-1-yl-phenyl)-amide]		0.0640
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-pyrazol-1-yl-phenyl)-amide]	0.0344	
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2-fluoro-4-pyrazol-1-yl-phenyl)-amide]		0.0434
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-[1,2,4]triazol-1-yl-phenl)-amide]		0.0619
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-[1,2,3]triazol-2-yl-phenyl)-amide]		0.1903
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-[1,2,3]triazol-1-yl-phenyl)-amide]		26% at 1 uM
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[(4-acetylamino-phenyl)-amide] 1-[(4-chloro-phenyl)-amide]		0.0793
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(cyclopentanecarbonyl-amino)-phenyl]-amide}		36% at 1 uM
4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-pyrimidin-5-yl-phenyl)-amide]		32% at 1 uM
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-pyrazol-1-yl-phenyl)-amide]		0.041000
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2-fluoro-4-pyrazol-1-yl-phenyl)-amide]		0.032000
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2-fluoro-4-pyrazol-1-yl-phenyl)-amide]		0.029000

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-pyrazol-1-yl-phenyl)-amide]		0.018000
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(3-methyl-pyrazol-1-yl)-phenyl]-amide}		0.082000
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(5-methyl-pyrazol-1-yl)-phenyl]-amide}		0.021000
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(5-methyl-pyrazol-1-yl)-phenyl]-amide}		0.009600
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(5-methyl-pyrazol-1-yl)-phenyl]-amide}		0.015000
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(3,5-dimethyl-pyrazol-1-yl)-phenyl]-amide}		0.049000
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(3.5-dimethyl-pyrazol-1-yl)-phenyl]-amide}		0.020000
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(3,5-dimethyl-pyrazol-1-yl)-2-fluoro-phenyl]-amide}		0.010000
(2R,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.010000
(2R,4R)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.025925
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.000770
(2R)-4-Hydroxyimino-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.002108
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methylsulfamoyl-biphenyl-4-yl)-amide]		0.001922
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-dimethylsulfamoyl-3-fluoro-biphenyl-4-yl)-amide]		0.001188
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-[(3-fluoro-2'-methane-sulfonyl-biphenyl-4-yl)-amide]		0.001021
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.000491
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-[(3-fluoro-2'-methane-sulfonyl-biphenyl-4-yl)-amide]		0.000701
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.000276

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
(2R,4S)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.001685
(2R,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.001200
(2R)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.005360
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 2-[(3-fluoro-2'-methane-sulfonyl-biphenyl-4-yl)-amide] 1-[(4-fluoro-phenyl)-amide]		0.001873
(2R,4R)-4-Acetylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.010545
(2R,4R)-4-Methanesulfonylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.001735
(2R,4S)-4-(1H-Tetrazol-5-yl)-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.038850
(2R,4S)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.011770
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-methyl-imidazol-1-yl)-phenyl]-amide}		0.006210
(2R,4R)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.055475
(2R,4R)-4-(1H-Tetrazol-5-yl)-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.007973
(2R,4R)-4-Trifluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.032950
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-cyano-3-fluoro-biphenyl-4-yl)-amide]		0.001950
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 2-[(2'-aminomethyl-3-fluoro-biphenyl-4-yl)-amide] 1-[(4-chloro-phenyl)-amide]		0.001633
(2R,4R)-4'-{[1-(4-Chloro-phenyl-carbamoyl)-4-methoxy-pyrrolidine-2-carbonyl]-amino}-3'-fluoro-biphenyl-2-carboxylic acid methyl ester		0.007112
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2,5-dihydro-pyrrole-1-carbonyl)-phenyl]-amide}		0.00029
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-dimethylcarbamoyl-2-fluoro-phenyl)-amide]		0.015
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.0081

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
Pyrrolidine-1,2-dicarboxylic acid 1-{(4-chloro-phenyl)-amide] 2-{[4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.081
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2-methyl-pyrrolidine-1-carbonyl)-phenyl]-amide}		0.024
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(ethyl-methyl-carbamoyl)-phenyl]-amide}		0.037
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-dimethylcarbamoyl-phenyl)-amide]		0.010
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2R-methyl-pyrrolidine-1-carbonyl)-phenyl]-amide}		0.011
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(2S-methyl-pyrrolidine-1-carbonyl)-phenyl]-amide}		0.082
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.0096
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(pyrrolidine-1-carbonyl)-2-pyrrolidin-1-yl-phenyl]-amide}		0.035
(2R,4R)-4-{[1-(4-Chloro-phenyl-carbamoyl)-4-hydroxy-pyrrolidine-2-carbonyl]-amino}-3-pyrrolidin-1-yl-benzoic acid methyl ester		0.020
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-{[4-(azetidine-1-carbonyl)-phenyl]-amide} 1-[(4-chloro-phenyl)-amide]		0.061
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.084
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.081
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-[(4-dimethylcarbamoyl-phenyl)-amide]		0.044
(2R,4R)-4-{[1-(4-Chloro-phenyl-carbamoyl)-4-hydroxy-pyrrolidine-2-carbonyl]-amino}-3-dimethylamino-benzoic acid methyl ester		0.029
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.0073
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-dimethylcarbamoyl-phenyl)-amide]		0.0049
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.0057
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-dimethylcarbamoyl-phenyl)-amide]		0.0039

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.0062
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-dimethylcarbamoyl-2-fluoro-phenyl)-amide]		0.0061
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenyl]-amide}		0.0044
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-dimethylcarbamoyl-2-fluoro-phenyl)-amide]		0.0029
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-methyl-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0052
(2R,4R)-4-Ethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-methyl-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.0020
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2-fluoro-4-quinolin-8-yl-phenyl)-amide]		0.066
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3,5-difluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.0098
Pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methane-sulfonyl-2-methyl-biphenyl-4-yl)-amide]		0.018
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.00073
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfinyl-biphenyl-4-yl)-amide]		0.0039
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(3-methyl-2'-methylsulfanyl-biphenyl-4-yl)-amide]		0.053
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.0012
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfonyl-3-methyl-biphenyl-4-yl)-amide]		0.00068
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methanesulfonyl-3-trifluoromethyl-biphenyl-4-yl)-amide]		0.0015
5-Methyl-4,5-dihydro-pyrazole-1,5-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 5-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.005623
3-Hydroxymethyl-4,5-dihydro-pyrazole-1,5-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 5-[(3-fluoro-2'-methane-sulfonyl-biphenyl-4-yl)-amide]		0.011267
4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 5-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.008015
(R) 4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 5-[(3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide]		0.007738

TABLE 1-continued

EXAMPLE	FXA 3 pM IC_{50} (mM)	FXA 30 pM IC_{50} (mM)
4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 5-{[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-amide}		0.044850
4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 5-[(3-fluoro-2'-methanesulfonyl-biphenyl-4-yl)-amide]		0.008718
1-(4-Chloro-phenylcarbamoyl)-5-(3-fluoro-2'-methanesulfonyl-biphenyl-4-ylcarbamoyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid ethyl ester		0.040850
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-methoxy-biphenyl-4-yl)-amide]		0.058900
(2R,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2'-hydroxy-biphenyl-4-yl)-amide]		0.074100
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(2-fluoro-4-iodo-phenyl)-amide]		0.058575
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.000404
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.001153
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(3-hydroxy-2-oxo-piperidin-1-yl)-phenyl]-amide}		0.008498
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-amide}		0.007665
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-imid-azolidin-1-yl)-phenyl]-amide}		0.036425
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide}		0.045525
(2R,4R)-1-(4-{[1-(4-Chloro-phenyl-carbamoyl)-4-methoxy-pyrrolidine-2-carbonyl]-amino}-3-fluoro-phenyl)-2-oxo-piperidine-3-carboxylic acid ethyl ester		0.011000
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(3-methoxy-2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.000862
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(3-methoxy-2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.005075
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[4-(3-methyl-2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.000383
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[4-(3-methyl-2-oxo-2H-pyridin-1-yl)-phenyl]-amide}		0.001793
(2R,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-[(4-morpholin-4-yl-phenyl)-amide]		0.043050