SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 06-22101

54. **TITULO** TIOFENOS SUSTITUIDOS Y SUS USOS

51. **CLASIFICACION INTERNACIONAL** C07D333/38, 409/12, A61K31/38, A61P35/00 // (C07D 409/12, 333:00) (C07D 409/12, 333:00, 307:00) (C07D 409/12, 333:00, 241:00)

71. **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SODERTALJE, SUECIA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

PETITORIO

AS: 100.478

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicacion : 06022101 00000000 Folios: 232
Fecha (AMD): 2006-03-06 16:14:08
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 15-03-2006

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: SE-151 85 Södertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: **JUAN PABLO CADENA SARMIENTO** Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Susan ASHWELL, Thomas GERO, Stephanos IOANNIDIS, James JANETKA, Paul LYNE, Vibha OZA, Stephanie SPRINGER, Mei SU, Dingwei YU **Dirección:** AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); 37 Village Green Drive, North Andover, MA 01845 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451, Estados Unidos de América (Respectivamente) **Nacionalidad o Domicilio:** Estados Unidos de América (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/GB2004/003473 Fecha 12-08-2004
Publicación Internacional No. WO 2005/016909 A1 Fecha 24-02-2005

Título (54): TIOFENOS SUSTITUIDOS Y SUS USOS

7 Clasificación Internacional (51) (C07D 333/38, 409/12, A61K 31/38, A61P 35/00 // (C07D 409/12, 333:00,) (C07D 409/12, 333:00, 307:00) (C07D 409/12, 333:00, 241:00)

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	15-08-2003	60/495,580
	US	28-05-2004	60/576,416

9 Comprobante de pago No. 06-4,820 **Fecha** 06-03-2006

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

2020-F06 (01-11-15)

2

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. **Fotocopia Autenticada**
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA: Juan Pablo Cadena

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

7

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06022181 00000000 Folios: 232
Fecha (AMD): 2006-03-06 16:14:08
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 4,820
FECHA : ENERO 23 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	45022890	23/01/2006	27,920,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRANITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $.	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

AS30049B

4

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 February 2005 (24.02.2005)

PCT

(10) International Publication Number
WO 2005/016909 A1

(51) International Patent Classification⁷: C07D 333/38, 409/12, A61K 31/38, A61P 35/00// (C07D 409/12, 333:00, 333:00) (C07D 409/12, 333:00, 307:00) (C07D 409/12, 333:00, 241:00)

(21) International Application Number: PCT/GB2004/003473

(22) International Filing Date: 12 August 2004 (12.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/495,580 15 August 2003 (15.08.2003) US
60/576,416 28 May 2004 (28.05.2004) US

(71) Applicant (*for all designated States except MG, US*): ASTRAZENECA AB [SE/SE]; SE-151 85 Södertälje (SE).

(71) Applicant (*for MG only*): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ASHWELL, Susan [GB/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). GERO, Thomas [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). IOANNIDIS, Stephanos [GR/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). JANETKA, James [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). LYNE, Paul [IE/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). OZA, Vibha [IN/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). SPRINGER, Stephanie [US/US]; 37 Village Green Drive, North Andover, MA 01845 (US). SU, Mei [CN/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). YU, Dingwei [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US).

(74) Agent: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, SE-151 85 Södertälje (SE).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, 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 (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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.

(54) Title: SUBSTITUTED THIOPHENES AND USES THEREOF

(57) Abstract: This invention relates to novel compounds having the structural formula (I) and to their pharmaceutical salts, compositions and methods of use. These novel compounds provide a treatment or prophylaxis of cancer.

WO 2005/016909 A1

SUBSTITUTED THIOPHENES AND USES THEREOF

Field of the Invention

The present invention relates to novel substituted thiophenes, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of cancers.

Background of the Invention

Chemotherapy and radiation exposure are currently the major options for the treatment of cancer, but the utility of both these approaches is severely limited by adverse effects on normal tissue, and the frequent development of tumor cell resistance. It is therefore desirable to improve the efficacy of such treatments in a way that does not increase the toxicity associated with them. One way to achieve this is by the use of specific sensitizing agents such as those described herein.

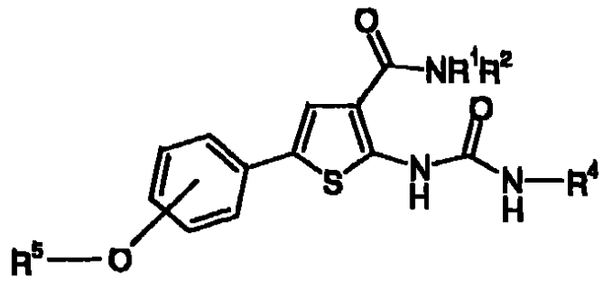
An individual cell replicates by making an exact copy of its chromosomes, and then segregating these into separate cells. This cycle of DNA replication, chromosome separation and division is regulated by mechanisms within the cell that maintain the order of the steps and ensure that each step is precisely carried out. Involved in these processes are the cell cycle checkpoints (Hartwell *et al.*, *Science*, Nov 3, 1989, 246(4930):629-34) where cells may arrest to ensure DNA repair mechanisms have time to operate prior to continuing through the cycle into mitosis. There are two such checkpoints in the cell cycle – the G1/S checkpoint that is regulated by p53 and the G2/M checkpoint that is monitored by the Ser/Thr kinase checkpoint kinase 1 (CHK1).

The cell cycle arrest induced by these checkpoints is a mechanism by which cells can overcome the damage resulting from radio- or chemotherapy, their abrogation by novel agents should increase the sensitivity of tumor cells to DNA damaging therapies. Additionally, the tumor specific abrogation of the G1/S checkpoint by p53 mutations in the majority of tumors can be exploited to provide tumor selective agents. One approach to the design of chemosensitizers

that abrogate the G2/M checkpoint is to develop inhibitors of the key G2/M regulatory kinase CHK1, and this approach has been shown to work in a number of proof of concept studies. (Koniaras *et al.*, *Oncogene*, 2001, 20:7453; Luo *et al.*, *Neoplasia*, 2001, 3:411; Busby *et al.*, *Cancer Res.*, 2000, 60:2108; Jackson *et al.*, *Cancer Res.*, 2000, 60:566).

Summary of the invention

Provided herein are novel compounds of structural formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 are at each occurrence independently selected from H, optionally substituted C_{1-6}alkyl, or optionally substituted heterocyclyl; with the proviso that R^1 and R^2 are not both H; or R^1 and R^2 and the N to which they are attached in combination form an optionally substituted heterocyclyl;

R^4 is selected from H, OH, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted C_{1-6}alkyl;

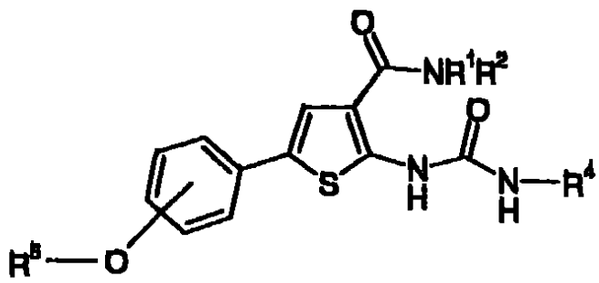
R^5 is selected from H, optionally substituted carbocyclyl, or optionally substituted C_{1-6}alkyl.

The invention also encompasses stereoisomers, enantiomers, *in vivo*-hydrolysable precursors and pharmaceutically-acceptable salts of compounds of formula I, pharmaceutical compositions and formulations containing them, methods of using them to treat diseases and

conditions either alone or in combination with other therapeutically-active compounds or substances, processes and intermediates used to prepare them, uses of them as medicaments, uses of them in the manufacture of medicaments and uses of them for diagnostic and analytic purposes.

Detailed Description of the Invention

Provided herein are novel compounds of structural formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor thereof:



(I)

wherein:

R^1 and R^2 are at each occurrence independently selected from H, optionally substituted C_{1-6}alkyl, or optionally substituted heterocyclyl; with the proviso that R^1 and R^2 are not both H; or R^1 and R^2 and the N to which they are attached in combination form an optionally substituted heterocyclyl;

R^4 is selected from H, OH, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted C_{1-6}alkyl;

R^5 is selected from H, optionally substituted carbocyclyl, or optionally substituted C_{1-6}alkyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^1 is an optionally substituted heterocyclyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^1 is an optionally substituted heterocyclyl wherein 1,2, or 3 substitutents is/are independently selected from halogen, nitro, amino, cyano, trifluoromethyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, hydroxy, alkylhydroxy, carbonyl, -CH(OH)CH_3, -CH_2NH-alkyl-OH, alkyl-(OH)CH_3, -CH_2-phenyl-(OCH_3)$_2$, -Oalkyl, -OCH_3, -Ophenyl, -OCOalkyl, -NHCHO, -Nalkyl, -N-(alkyl)-CHO, -NH-CO-amino, -N-(alkyl)-CO-amino, -NH-COalkyl, -N-(alkyl)-COalkyl, -carboxy, -amidino, -CO-amino, -CO-alkyl, -CO_2alkyl, mercapto, -Salkyl, -SCH_2furanyl, -SO(alkyl), -SO_2(alkyl), -SO_2-amino, -alkylsulfonylamino, phenyl, anisole, dimethoxyphenyl, trimethoxyphenyl, halophenyl, cycloalkyl, heterocyclyl, -alkyl-NH-cycloalkyl, -alkyl-NH- heterocyclyl, -alkyl-NH-alkyl-OH, -C(=O)OC(CH_3)$_3$, -N(CH_3)$_2$, -N(CH_2CH_3)$_2$, -alkyl-NH-alkyl- heterocyclyl, -alkyl-aryl, -methyl-phenyl, alkyl-polycyclyl, alkyl-amino, alkyl-hydroxy, -CH_2NH-alkyl-heterocyclyl, -CH_2NHCH2CH(CH_3)$_2$, vicinal -O(alkyl)O-, vicinal -OC(haloalkyl)O-, vicinal -CH_2O(alkyl)O-, vicinal -S(alkyl)S- and –O(alkyl)S-.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^1 is an optionally substituted heterocyclyl wherein 1,2, or 3 substitutents is/are independently selected from: -OH, C(=O)OC(CH_3)$_3$, NH_2, C_{1-6}alkyl, methoxybenzene, or dimethoxy benezene.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^1 is a heterocyclyl wherein heterocyclyl is selected from piperdinyl, pyridinyl, pyrrolidinyl, pyrazinyl, azepanyl, azetidinyl, azabicyclozinyl, furanyl, thienyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^2 is H.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^4 is H.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^5 is H or an optionally substituted C_{1-6}alkyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^5 is H or an optionally substituted C_{1-6}alkyl wherein 1,2 or 3 substitutents is/are independently selected from: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH3, OH, -C_{1-6}alkyl, morpholino, piperidinyl, pyrrolodinyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^5 is H or an optionally substituted C_{1-3}alkyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein R^5 is H or an optionally substituted C_{1-3}alkyl wherein 1,2 or 3 substitutents is/are independently selected from: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH3, OH, -C_{1-6}alkyl, morpholino, piperidinyl, pyrrolodinyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein

R^1 is an optionally substituted heterocyclyl;

R^2 is H;

R^4 is H;

R^5 is H or an optionally substituted C_{1-6}alkyl.

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One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein:

R^1 is an optionally substituted heterocyclyl wherein the substitutent is selected from one or more of the following: $-NH_2$, C_{1-6}alkyl, $-C(=O)OC(CH_3)_3$,

R^2 is H;

R^4 is H;

R^5 is H or an optionally substituted C_{1-6}alkyl wherein the substitutent is selected from one or more of the following: $-C_{1-6}$alkyl, $-N(C_{1-3}alkyl)_2$.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein:

R^1 is an optionally substituted heterocyclyl wherein the substitutent is selected from one or more of the following: $-NH_2$, C_{1-6}alkyl, $-C(=O)OC(CH_3)_3$,

R^2 is H;

R^4 is H;

R^5 is H or an optionally substituted C_{1-3}alkyl wherein 1,2 or 3 substitutents is/are independently selected from: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH3, OH, $-C_{1-6}$alkyl, morpholino, piperidinyl, pyrrolodinyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein:

R^1 is a heterocyclyl;

R^2 is H;

R^4 is H;

R^5 is H or a C_{1-6}alkyl.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt or an *in vivo*-hydrolysable precursor wherein:

R^1 is a 6-membered heterocyclyl containing at least one N in the ring;

R^2 is H;

R^4 is H;

R^5 is a C_{1-3}alkyl.

One embodiment of the present invention provides compounds of formula (I) selected from the following:

tert-butyl 3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide;

tert-butyl 3-{[(2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[(3R)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-{4-[2-(diethylamino)ethoxy]phenyl}-2-thienyl)urea;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(2-aminoethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-pyridin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1-methylpiperidin-4-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylazepan-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-pyridin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-pyrrolidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[2-(dimethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[2-(diethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(piperidin-4-ylmethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(1-ethylpiperidin-3-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[(3S)-1-ethylazepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(3-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

tert-butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)pyrrolidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(1-benzylpiperidin-4-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-azetidin-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(2S)-pyrrolidin-2-ylmethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyridin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperidin-1-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-1-azabicyclo[2.2.2]oct-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(2-hydroxyethyl)-5-(4-hydroxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(trans-4-hydroxycyclohexyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(2-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(tetrahydrofuran-2-ylmethyl)thiophene-3-carboxamide;

tert-butyl (3R)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-3-ylmethyl)thiophene-3-carboxamide;

tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azetidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-4-ylmethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(3-methoxypropyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]urea;

2-[(aminocarbonyl)amino]-N-(2-methoxyethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-{2-[(2-furylmethyl)thio]ethyl}-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide;

N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-{3-[2-(diethylamino)ethoxy]phenyl}-2-thienyl)urea;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1,2,3,4-tetrahydroquinolin-3-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(1,3-benzodioxol-5-ylmethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(3-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(5-methyl-2-furyl)methyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-2-ylmethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(4-fluorobenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-N-(2-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-phenoxyethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-2-ylethyl)thiophene-3-carboxamide;

tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-N-(4-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide;

tert-butyl (3S)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxamide;

tert-butyl (3R)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

N-[3-{[(3S)-3-aminoazepan-1-yl]carbonyl}-5-(4-methoxyphenyl)-2-thienyl]urea;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

tert-butyl 3-{[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea;

N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea;

tert-butyl 4-{[(5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

tert-butyl 3-{[(5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

5-[4-(2-diethylamino-ethoxy)-phenyl]-2-(3-hydroxy-urea)-thiophene-3-carboxylic acid-(S)-piperidin-3-ylamide;

2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(3-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(2-hydroxyphenyl)-*N*-[(3S)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-[2-(benzyloxy)phenyl]-*N*-[(3S)-piperidin-3-yl]thiophene-3-carboxamide.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt thereof for use as a medicament.

One embodiment of the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with cancer.

One embodiment of the present invention provides a method for the treatment of cancer comprising administering to a human a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

One embodiment of the present invention provides a method for the treatment of breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma by administering a compound of formula I or a pharmaceutically acceptable salt thereof.

One embodiment the of present invention provides a method of treating cancer by administering to a human a compound of formula (I) or a pharmaceutically acceptable salt thereof and an anti-tumor agent.

One embodiment of the present invention provides a method of treating cancer by administering to a human a compound of formula (I) or a pharmaceutically acceptable salt thereof and a DNA damaging agent.

One embodiment of the present invention provides a method for the treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

One embodiment of the present invention provides a method for the prophylaxis treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

One embodiment of the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier, diluent or excipent.

One embodiment of the present invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises:

(a) the reaction of a 2-aminothiophene shown below as formula II

19

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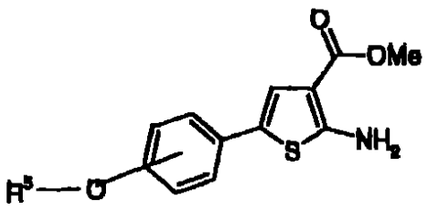
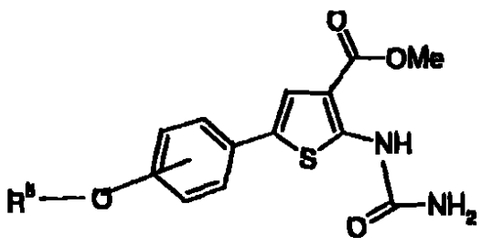


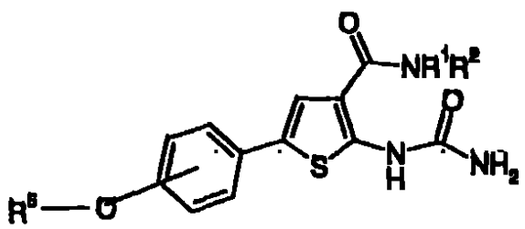
II

wherein the hydrogen at the 2-amino position is displaced to form an amide, shown as formula III below



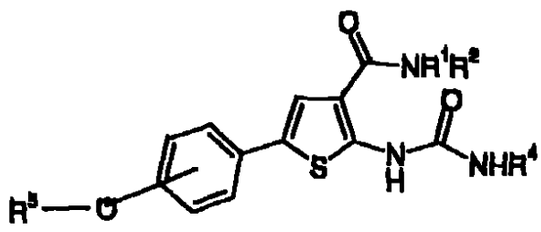
III

wherein the methyl ester is converted to an amide utilizing the desired amine in conjunction with an aluminate organometallic complex, to give the product shown as formula IV below:



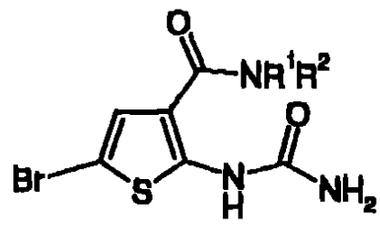
IV

wherein the amide is converted to various substituted secondary ureas by the reaction with various isocyanantes to yield the product shown as formula V below:



V

One embodiment of the present invention provides the use of a compound of formula (VI) below or a pharmaceutically acceptabl salt or an in vivo hydrolysable precursor in the manufacture of a compound of formula (I).



VI

The definitions set forth in this application are intended to clarify terms used throughout this application. The term "herein" means the entire application.

As used in this application, the term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted. In the event a substitution is desired then such substitution means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the normal valency of the designated atom is not exceeded, and that the substitution results in a stable compound. For example when a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Examples of such substituents are as follows:
halogen, nitro, amino, cyano , trifluoromethyl, C_{1-6}alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, hydroxy, alkylhydroxy, carbonyl, $-CH(OH)CH_3$, $-CH_2NH$-alkyl-OH, alkyl-$(OH)CH_3$, $-CH_2$-phenyl-$(OCH_3)_2$, -Oalkyl, $-OCH_3$, -Ophenyl, -OCOalkyl, -NHCHO, -N-(alkyl)-CHO, -Nalkyl, -NH-CO-amino, -N-(alkyl)-CO-amino, -NH-COalkyl, -N-(alkyl)-COalkyl, -carboxy, -amidino, -CO-amino, -CO-alkyl, $-CO_2$alkyl, mercapto, -Salkyl, $-SCH_2$furanyl, -SO(alkyl), $-SO_2$(alkyl), $-SO_2$-amino, -alkylsulfonylamino, phenyl, anisole, dimethoxyphenyl, trimethoxyphenyl, halophenyl, cycloalkyl, heterocyclyl, -alkyl-NH-cycloalkyl, -alkyl-NH- heterocyclyl, -alkyl-NH-alkyl-OH, $-C(=O)OC(CH_3)_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, -alkyl-NH-alkyl- heterocyclyl, -alkyl-aryl, -methyl-phenyl, alkyl-polycyclyl, alkyl-amino, alkyl-hydroxy, $-CH_2NH$-alkyl-heterocyclyl, $-CH_2NHCH2CH(CH_3)_2$.

If the selection is attached to a ring the substituents could also be selected from: vicinal -O(alkyl)O-, vicinal -OC(haloalkyl)O-, vicinal -CH_2O(alkyl)O-, vicinal -S(alkyl)S- and –O(alkyl)S-.

A variety of compounds in the present invention may exist in particular geometric or stereoisomeric forms. The present invention takes into account all such compounds, including cis- and trans isomers, R- and S- enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as being covered within the scope of this invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention. The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by syntheals from optically active starting materials. When required, separation of the racemic material can be achieved by methods known in the art. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" used alone or as a suffix or prefix, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. As used herein, "C_{1-3} alkyl", whether a terminal substituent or an alkylene group linking two substituents, is understood to specifically include both branched and straight-chain methyl, ethyl, and propyl.

As used herein "alkylhydroxy" represents an alkyl group straight chain or branched as defined above with the indicated number of carbon atoms with one or more hydroxy groups attached. One such example of alkylhydroxy would be $-CH_2OH$.

As used herein, the term "carbocyclyl" is intended to include both alicyclic and aromatic ring structures wherein the closed ring is made of carbon atoms. These may include fused or bridged polycyclic systems. Carbocyclyls may have from 3 to 10 carbon atoms in their ring structure, and often have 3, 4, 5, and 6 carbons in the ring structure. For example, "C_{3-6} carbocyclyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopenta-diene or phenyl.

As used herein, the term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. These may include fused or bridged polycyclic systems. Preferred cycloalkyls have from 3 to 10 carbon atoms in their ring structure, and more preferably have 3, 4, 5, and 6 carbons in the ring structure. For example, "C_{3-6} cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, "alkenyl" or "alkenylene" is intended to include from 2 to 12 hydrocarbon atoms of either a straight or branched configuration with one or more carbon-carbon double bonds that may occur at any stable point along the chain. Examples of "C_{3-6}alkenyl" include, but

are not limited to, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, hexenyl.

As used herein, "alkynyl" or "alkynylene" is intended to include from 2 to 12 hydrocarbon chains of either a straight or branched configuration with one or more carbon-carbon triple bonds that may occur at any stable point along the chain. Examples of alkynyl include but are not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl.

As used herein, the term "alkylcycloalkyl" is intended to mean an alkyl attached to the formula atom modified with a cycloalkyl. Examples of alkylcycloalkyl include, but are not limited to cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl.

As used herein, "cycloalkenyl" refers to ring-containing hydrocarbyl groups having at least one carbon-carbon double bond in the ring, and having from 3 to 12 carbons atoms.

As used herein, "cycloalkynyl" refers to ring-containing hydrocarbyl groups having at least one carbon-carbon triple bond in the ring, and having from 7 to 12 carbons atoms..

As used herein, the term "aralkyl" refers to an alkyl group substituted with an aryl group (an aromatic or heteroaromatic group).

As used herein, "aromatic" refers to hydrocarbyl groups having one or more polyunsaturated carbon rings having aromatic character, (e.g., 4n + 2 delocalized electrons) and comprising up to about 14 carbon atoms.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, furan, imidazole, isoxazole, nicotinic, isonicotinic, oxazole, phenyl, pyrazole, pyrazine, pyridazine, pyridine,

pyrimidine, thiazole, thiophene, triazole and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "heteroaryl" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, for example, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.
The terms ortho, meta and para apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

As used herein, the term "heterocyclyl" or "heterocyclic" or "heterocycle" refers to a ring-containing monovalent and divalent structures having one or more heteroatoms, independently selected from N, O and S, as part of the ring structure and comprising from 3 to 20 atoms in the rings, more preferably 3- to 7- membered rings. Heterocyclic groups may be saturated or unsaturated, containing one or more double bonds, and heterocyclic groups may contain more than one ring as in the case of polycyclic systems. The heterocyclic rings described herein may be substituted on carbon or on a heteroatom atom if the resulting compound is stable. If specifically noted, nitrogen in the heterocyclyl may optionally be quaternized. It is understood that when the total number of S and O atoms in the heterocyclyl exceeds 1, then these heteroatoms are not adjacent to one another.

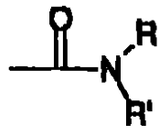
Examples of heterocyclyls include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H, 6H-1, 5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1, 2,5-thiadiazinyl, acridinyl, azabicyclo, azetidine, azepane, aziridine, azocinyl, benzimidazolyl, benzodioxol, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, diazepane, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dioxolane, furyl, 2,3-dihydrofuran, 2,5-dihydrofuran, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, homopiperidinyl, imidazolidine, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl,

indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxirane, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, purinyl, pyranyl, pyrrolidinyl, pyrroline, pyrrolidine, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, N-oxide-pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, pyridine, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroquinoline, tetrahydroisoquinolinyl, thiophane, thiotetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiopheneyl, thiirane, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (for example, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and /or heterocyclyls) in which two or more carbons are common to two adjoining rings, for example, the rings are "fused rings." Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, carbonyl, carboxyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like. Examples of such bridged heterocyclyls include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane, substituted piperazine.

As used herein, the term "amine" or "amino" refers to groups of the general formula – NRR', wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Example of the amino group include, but are not limited to NH_2, methylamine, ethylamine, dimethylamine, diethylamine, propylamine, benzylamine and the like.

As used herein, the term "amido" is art-recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:

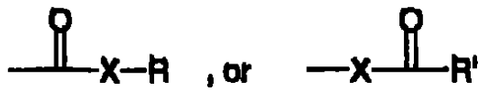


wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heteroaralkyl, or R and R' may form a ring.

As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, n-pentoxy, isopentoxy, cyclopropylmethoxy, allyloxy and propargyloxy. Similarly, "alkylthio" or "thioalkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the term "acyl" refers to groups of the of the general formula –C(=O)-R, wherein R is hydrogen, hydrocarbyl radical. Examples of acyl groups include, but are not limited to acetyl, propionyl, benzoyl, phenyl acetyl.

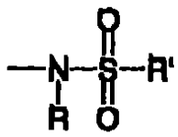
As used herein, the term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or sulfur, and R represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R''$ or a pharmaceutically acceptable salt, R' represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R''$, where m is an integer less than or equal to ten, and R'' is alkyl, cycloalkyl, alkenyl, aryl, or heteroaryl. Where X is an oxygen and R and R' is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R is as defined above, the moiety is

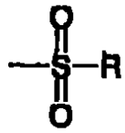
referred to herein as a carboxyl group, and particularly when R' is a hydrogen, the formula represents a "carboxylic acid." Where X is oxygen, and R' is a hydrogen, the formula represents a "formate." In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R and R' is not hydrogen, the formula represents a "thiolester." Where X is sulfur and R is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is sulfur and R' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R is not a hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R is hydrogen, the above formula is represents an "aldehyde" group.

As used herein, the term "sulfonylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heteroaralkyl.

As used herein, the term "sulfonyl" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R is represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, aralkyl, or heteroaralkyl.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, tosylate, benezensulfonate, and the like.

As used herein, "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, heptafluoropropyl, and heptachloropropyl. "Haloalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge; for example trifluoromethoxy, pentafluoroethoxy, 2,2,2-trifluoroethoxy, and the like. "Haloalkylthio" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the phrase-protectingprotecting group" means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999).

As used herein, "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional

non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, phosphoric, and the like; and the salts prepared from organic acids such as lactic, maleic, citric, benzoic, methanesulfonic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

As used herein, "in vivo hydrolysable ester" means an in vivo hydroysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy or a hydroxy group. For example amino acid esters, C_{1-6} alkoxymethyl esters like methoxymethyl; C_{1-6}alkanoyloxymethyl esters like pivaloyloxymethyl; C_{3-8}cycloalkoxycarbonyloxy C_{1-6}alkyl esters like 1-cyclohexylcarbonyloxyethyl, acetoxymethoxy, or phosphoramidic cyclic esters.

As used herein "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The anti-cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents:

(i) antiproliferative/antineoplastic/DNA damaging drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas);

antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin) and cytodifferentiating agents (for example All-trans retinoic acid, 13-cis retinoic acid and fenretinide);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (Cl 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in published International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds

that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention.

Compounds of the present invention may be administered orally, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

An effective amount of a compound of the present invention for use in therapy of infection is an amount sufficient to symptomatically relieve in a warm-blooded animal, particularly a human the symptoms of infection, to slow the progression of infection, or to reduce in patients with symptoms of infection the risk of getting worse.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers include magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Some of the compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, phosphoric, and the like; and the salts prepared from organic acids such as lactic, maleic, citric, benzoic, methanesulfonic, trifluoroacetate and the like.

In one embodiment a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

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In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The term composition is intended to include the formulation of the active component or a pharmaceutically acceptable salt with a pharmaceutically acceptable carrier. For example this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

Liquid form compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided 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 the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Compounds of formula (I) have been shown to inhibit checkpoint kinase activity in vitro. Inhibitors of checkpoint kinase have been shown to allow cells to progress inappropriately to the metaphase of mitosis leading to apoptosis of effected cells, and to therefore have anti-proliferative effects. Therefore it is believed that the compounds of formula (I) may be used for

the treatment of neoplastic disease. Hence compounds of formula (I) and their salts are expected to be active against neoplastic disease such as carcinoma of the brain, breast, ovary, lung, colon, prostate, skin or other tissues, as well as leukemias and lymphomas, tumors of the central and peripheral nervous system, and other tumor types such as melanoma, sarcomas, fibrosarcoma and osteosarcoma. In addition, compounds of formula (I) are also expected to be useful for the treatment other proliferative diseases. It is expected that the compounds of formula (I) would most likely be used in combination with a broad range of DNA damaging agents but could also be used as a single agent.

Generally, the compounds of formula (I) have been identified in one or both assays described below as having an IC_{50} value of 100 micromolar or less. For example compound of example 2 has an IC_{50} value of 10 nM.

Checkpoint Kinase 1 Assay: This in vitro assay measures the inhibition of CHK1 kinase by compounds. The kinase domain is expressed in baculovirus and purified by the GST tag. Purified protein and biotinylated peptide substrate (Cdc25C) is then used in a 384 well automated Scintillation Proximity Assay (SPA). Specifically, peptide, enzyme and reaction buffer are mixed and aliquoted into a 384 well plate containing dilution series of compounds and controls. Cold and hot ATP are then added to initiate the reaction. After 2 hours, a SPA bead slurry, CsCl2 and EDTA are added to stop the reaction and capture the biotinylated peptide. Plates are then counted on a Topcount. Data is analyzed and IC50s determined for individual compounds.

Abrogation Assay: This cellular assay measures the ability of CHK1 inhibitors to abrogate the DNA-damage induced G2/M checkpoint. Compounds active against the enzyme (< 2 uM) are tested in the cellular assay. Briefly HT29 cells (colon cancer cell line, p53 null) are plated in 96 well plates on day 1. The following day, cells are treated with camptothecin for 2 hours to induce DNA damage. After 2 hours, camptothecin is removed and cells are treated for an additional 18 hours with test compound and nocodazole, a spindle poison that traps in cells in mitosis that abrogate the checkpoint. Cells are then fixed with formaldehyde, stained for the presence of phosphohistone H3, a specific marker for mitosis and labeled with Hoechst dye so that cell number can be measured. Plates are scanned using the Mitotic Index protocol on the Array Scan (Cellomics). As a positive control for abrogation, 4 mM caffeine is used.

Compounds are tested in a 12-point dose response in triplicate. Data is analyzed and EC50s determined for individual compounds.

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Such methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described herein. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are not compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must then be used.

The starting materials for the examples contained herein are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials and examples used herein.

General procedures for making the compounds of the invention is as follows:

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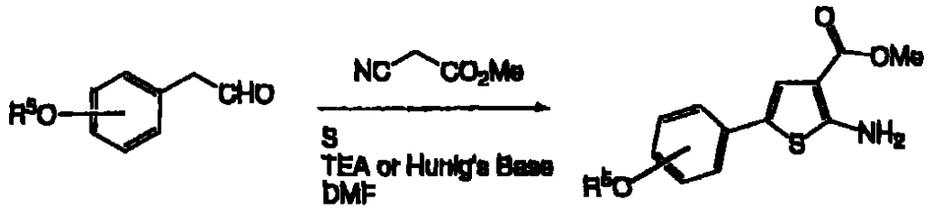
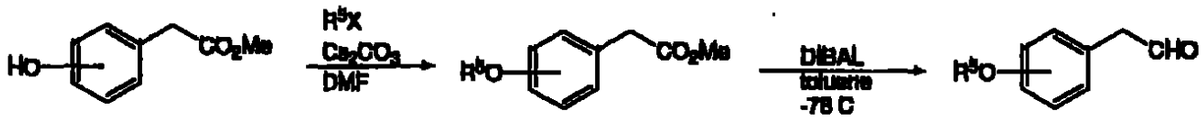
The first of these procedures initiates from a common intermediate. This intermediate 2-aminothiophene core is produced by a one-pot Gewald synthesis from reaction of cyanomethylacetate with various benzaldehydes and elemental sulfur under basic conditions shown below in Scheme I.



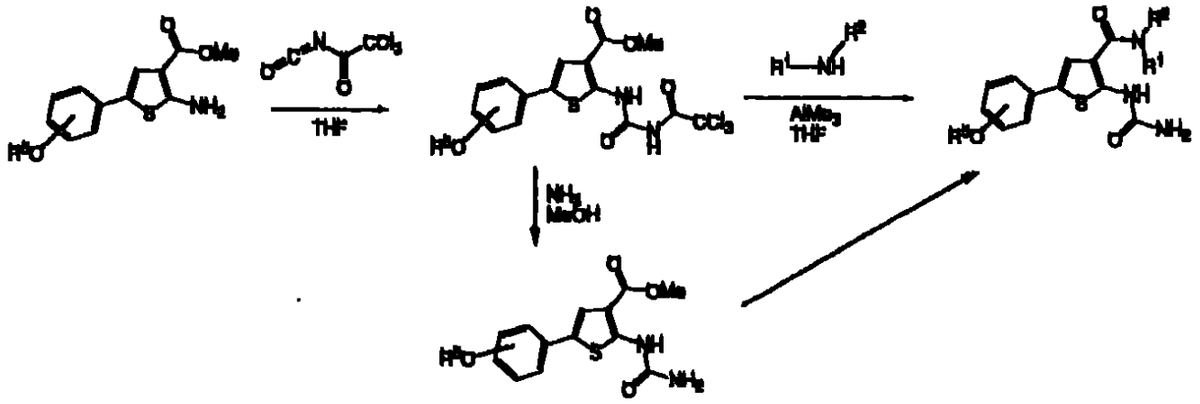
Scheme I

If not commercially available, the corresponding benzaldehydes could be synthesized using some or all of the transformations described in Scheme II.



Scheme II

Compounds of Formula (I) can then be synthesized from the general synthetic methods described below in Schemes III-IX. The first general method shown in Scheme III involves a Weinreb amide formation from reaction of either the trichloroacetyl-protected or free urea with an amino aluminate organometallic complex.



Scheme III

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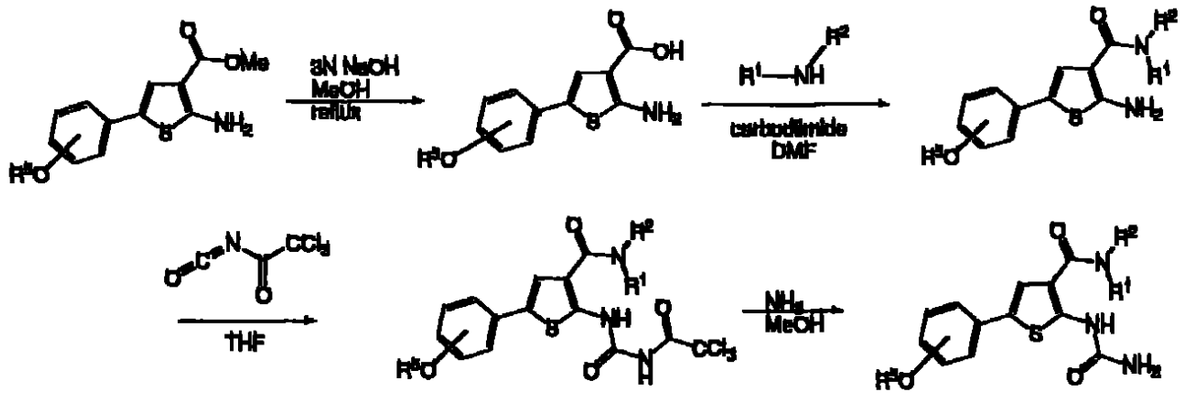
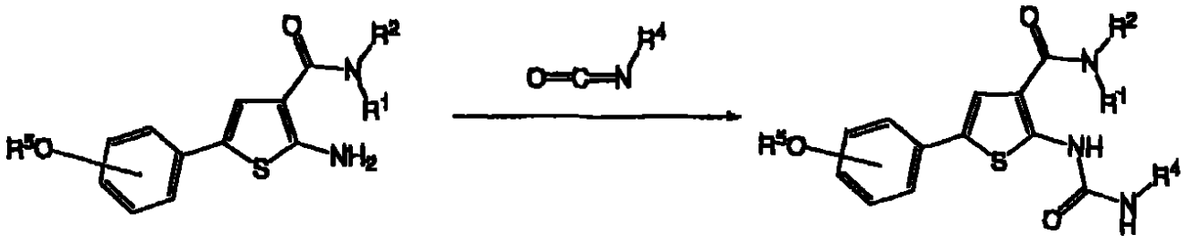
An alternate method for the generation of similar compounds is described in Scheme IV. This general route utilizes the same starting 2-aminothiophene ester from Scheme III but amide bond formation is executed from the reaction of the corresponding carboxylic acids with various amines. A variety of coupling agents can be used to effect this transformation including EDCI, DIC, BOP, and HATU under standard coupling methods very familiar to those practicing and trained in the art of organic synthesis. Generation of the final primary urea is then performed using a simple two-step reaction with trichloroacetylisocyanate followed by cleavage with ammonia in methanol.

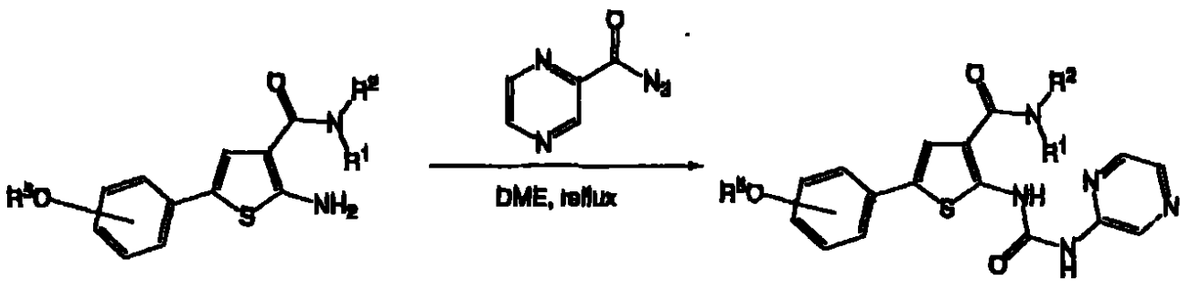


Scheme IV

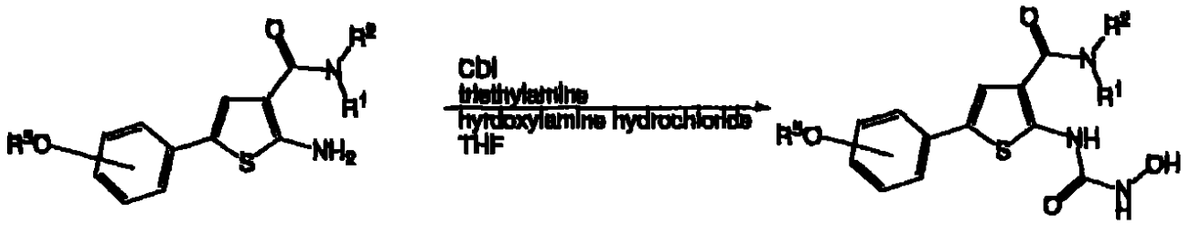
As shown in the following Schemes V-VII, the amide product formed prior to urea generation in Scheme IV can be used as a common intermediate for the formation of various substituted ureas where R^4 is not hydrogen. Reaction with isocyanantes, acyl azides (in particular pyrazine acyl azides), or carbonyldiimidazole and amines (in particular hydroxylamine hydrochloride), leads to the creation of various substituted secondary ureas where R^4 is selected from OH, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted C_{1-6}alkyl.



Scheme V

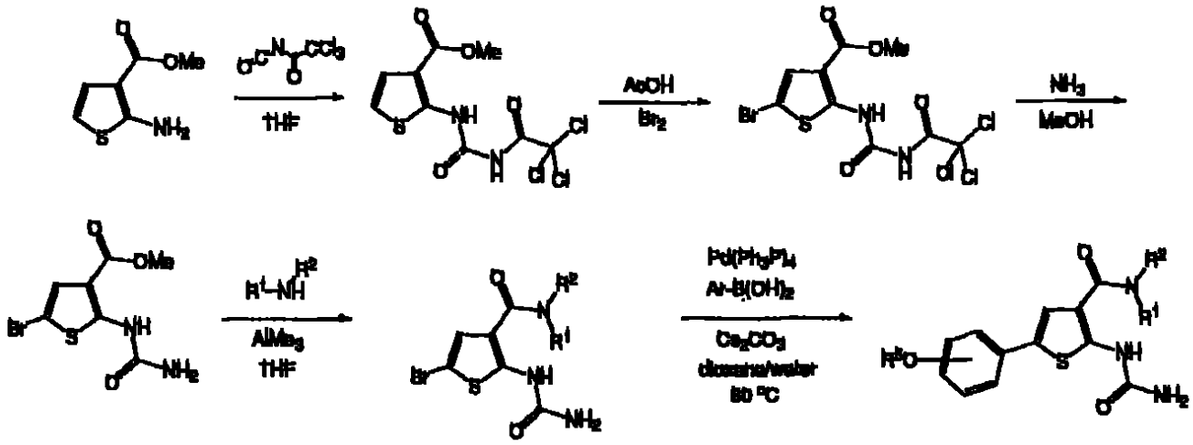


Scheme VI



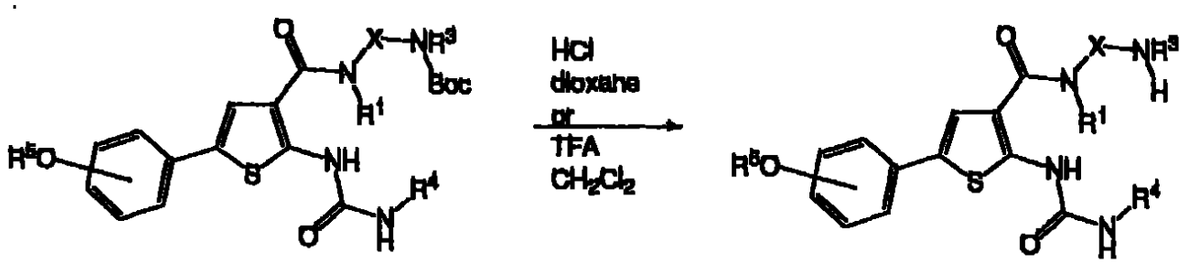
Scheme VII

An additional general process presented in this invention involves an improvement on the construction of general compounds with formula (I). The method, which employs a Suzuki Coupling of a 5-bromothiophene intermediate as its key transformation, is shown in Scheme VIII. This method allows for increased diversity much later in the synthesis and is amenable to parallel combinatorial methods of organic synthesis. Commercially available 2-amino-thiophene-3-carboxylic acid methyl ester is protected as the trichloroacetyl urea, followed by selective bromination at the 5-position with bromine in acetic acid. Removal of the protecting group with ammonia in methanol, followed by Weinreb amidation yields the common intermediate. Standard Suzuki reaction conditions are then employed to finally generate the target compounds.



Scheme VIII

If the final compound generated from any of the above-mentioned methods or schemes has a protecting group on nitrogen (in particular a carbamate) or oxygen (in particular an ether or ester) present anywhere on the molecule standard methods of removal can be utilized to generate final compounds. Shown in Scheme IX is the general method used for the deprotection of a tert-butoxycarbonyl carbamate to yield the secondary amine product (R^2=XNHR^3) as the corresponding hydrochloride or trifluoroacetate salt. Cleavage of methyl ethers to phenols (not shown) is affected by reaction with boron tribromide in methylene chloride. Both of these methods are very familiar with those trained in the art of organic synthesis.



Scheme IX

Examples:

Table 1

IUPAC Name	Ex.	LCMS (M+1, ES or APCI detection)	^{1}H NMR (d_6-DMSO unless stated otherwise)	Synthesis Method (Scheme)
tert-butyl 3-[[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	1	560	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(m, 2H), 3.90(m, 3H), 3.60(m, 2H), 3.30(m, 4H), 2.95(dd, 2H), 2.10(m, 1H), 1.80(m, 1H), 1.50(m, 2H), 1.40(s, 9H), 1.35(t, 6H)	III
2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide trifluoroacetate	2	460		III
2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide trifluoroacetate	3	460		III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	4	376	1.76-1.49 (m, 2H), 1.93 (brs, 2H), 2.85 (t, 2H), 3.18 (s, 1H), 3.22 (brd, 1H), 3.31 (brd, 1H), 3.77 (s, 3H), 4.11 (brs, 1H), 6.97 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.99 Hz), 7.56 (s, 1H), 8.02 (d, 1H), J=7.33 Hz), 8.85 (brs, 2H), 10.81 (s, 1H)	III
tert-butyl 3-[[(2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	5	560	MeOD; 7.85(d, 1H), 7.30(dd, 2H), 7.20(s, 1H), 6.90(d, 1H), 4.35(m, 2H), 3.90(m, 2H), 3.60(m, 2H), 3.30(m, 4H), 3.00(m, 2H), 2.10(m, 1H), 1.80(m, 1H), 1.60(m, 2H), 1.45(s, 9H), 1.40(t, 6H)	III
2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide	6	460	MeOD; 7.52(d, 2H), 7.45(s, 1H), 7.01(d, 2H), 4.35(m, 2H), 3.90(m, 2H), 3.48(m, 1H), 3.42(m, 2H), 3.33(q, 4H), 3.13(m, 2H), 2.14(m, 2H), 1.85(m, 2H), 1.35(t, 6H)	III
2-[(aminocarbonyl)amino]-N-[(3R)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	7	389	CDCl3; 11.30(br s, 1H), 7.50 (d, 2H), 7.05(d, 1H), 7.00 (s, 1H), 6.85(d, 2H), 5.15 (s, 2H), 4.20(m, 1H), 3.80(s, 3H), 3.10 (m, 1H), 3.00 (m, 2H), 2.80 (m, 1H), 1.80(m, 2H), 1.70(m, 3H), 1.50 (m, 1H)	III

N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-[4-[2-(diethylamino)ethoxy]phenyl]-2-thienyl)urea trifluoroacetate	8	460	MeOD; 7.43(d, 2H), 6.93(d, 2H), 6.92(s, 1H), 4.33(m, 2H), 4.27(dd, 2H), 3.52(dd, 2H), 3.32(m, 1H), 3.24(q, 4H), 3.02(m, 2H), 1.99(m, 1H), 1.95(m, 1H), 1.47(m, 2H), 1.27(t, 6H)	III
2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide trifluoroacetate (salt)	9	483	MeOD; 7.81(m, 1H), 7.57(s, 1H), 7.49(m, 1H), 7.47(d, 2H), 7.23(t, 1H), 7.03(dd, 1H), 6.93(d, 2H), 4.62(s, 2H), 4.27(dd, 2H), 4.31(dd, 2H), 3.24(q, 4H), 1.27(t, 6H)	III
2-[(aminocarbonyl)amino]-5-[3-[2-(diethylamino)ethoxy]phenyl]-N-piperidin-4-ylthiophene-3-carboxamide trifluoroacetate	10	460	MeOD; 7.62(s, 1H), 7.29(dd, 1H), 7.24(m, 1H), 7.13(m, 1H), 6.87(m, 1H), 4.35(dd, 2H), 3.59(dd, 2H), 3.46(m, 1H), 3.40(m, 2H), 3.31(q, 4H), 3.10(m, 2H), 2.16(m, 2H), 1.83(m, 2H), 1.34(t, 6H)	III
2-[(aminocarbonyl)amino]-N-(2-aminoethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	11	335	MeOD; 7.38(d, 2H), 7.36(s, 1H), 6.82(d, 2H), 3.70(s, 3H), 3.57(dd, 2H), 3.10(dd, 2H),	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	12	375	1.70 (m, 2H), 1.99 (d, 2H, J=12.88 Hz), 3.01 (q, 2H, J=11.03 Hz), 3.35 (d, 2H, J=12.38 Hz), 3.76 (s, 3H), 4.01 (brs, 1H), 6.97 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.84 Hz), 7.63 (s, 1H), 8.04 (d, 1H, J=7.07 Hz), 8.43 (d, 1H, J=9.10 Hz), 8.65 (d, 1H, J=8.59 Hz), 10.91 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-[3-[2-(diethylamino)ethoxy]phenyl]-N-pyridin-3-ylthiophene-3-carboxamide trifluoroacetate	13	454	MeOD; 9.51(s, 1H), 8.75(d, 1H), 8.51(m, 1H), 7.97(s, 1H), 7.93(m, 1H), 7.35(t, 1H), 7.29(m, 2H), 6.93(m, 1H), 4.45(dd, 2H), 3.67(dd, 2H), 3.39(q, 4H), 1.42(t, 6H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1-methylpiperidin-4-yl)thiophene-3-carboxamide	14	389	1.76 (q, 2H), 2.04 (d, 2H, J=12.38 Hz), 2.77 (brd, 3H), 3.08 (q, 2H), 3.48 (d, 2H, J=11.62 Hz), 3.76 (s, 3H), 3.96 (m, 1H), 6.97 (d, 2H), 7.45 (d, 2H, J=8.84 Hz), 7.63 (s, 1H), 8.07 (d, 1H, J=7.33 Hz), 9.62 (brs, 1H), 10.91 (s, 1H)	III

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylazepan-3-yl]thiophene-3-carboxamide hydrochloride	15	403	CDCl3; 11.35(br s, 1H), 7.50 (d, 2H), 7.15(d, 1H), 6.95 (s, 1H), 6.90(d, 2H), 5.30 (s, 2H), 4.20(m, 1H), 3.80(s, 3H), 2.85 (m, 1H), 2.80 (d, 1H), 2.60 (dd, 1H), 2.40(m, 1H), 2.45(s, 3H), 1.50-2.00 (m, 8H)	III
2-[(aminocarbonyl)amino]-5-[3-[2-(diethylamino)ethoxy]phenyl]-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide trifluoroacetate (salt)	16	483	MeOD; 7.84(s, 1H), 7.75(m, 1H), 7.63(dd, 1H), 7.35(t, 2H), 7.32(m, 1H), 7.22(m, 1H), 7.16(dd, 1H), 6.92(m, 1H), 4.65(s, 2H), 4.41(dd, 2H), 3.53(dd, 2H), 3.37(q, 4H), 1.40(t, 6H)	III
2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-N-pyrrolidin-3-ylthiophene-3-carboxamide trifluoroacetate	17	448	MeOD; 7.46(d, 2H), 7.16(s, 1H), 6.95(d, 2H), 4.28(dd, 2H), 3.69(m, 3H), 3.70 (m, 2H), 3.53(dd, 2H), 3.28(q, 4H), 2.30(m, 1H), 2.09(m, 1H), 1.29(t, 6H)	III
2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-N-pyridin-3-ylthiophene-3-carboxamide trifluoroacetate	18	454	MeOD; 9.56(s, 1H), 8.75(d, 1H), 8.58(d, 1H), 8.00(m, 2H), 7.71(s, 1H), 7.59(d, 2H), 7.07(d, 2H), 4.41(dd, 2H), 3.65(dd,2H), 3.38(q, 4H), 1.40(t, 6H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]thiophene-3-carboxamide hydrochloride	19	389	CDCl3; 11.25(br s, 1H), 7.50 (d, 2H), 7.15(s, 1H), 6.85 (d, 2H), 6.90(m, 2H), 5.40 (s, 2H), 4.25(m, 1H), 3.80(s, 3H), 2.40-2.80 (m, 4H), 2.30(s, 3H), 2.20(m, 1H), 1.50-1.90 (m, 3H)	III
2-[(aminocarbonyl)amino]-5-[3-[2-(diethylamino)ethoxy]phenyl]-N-pyrrolidin-3-ylthiophene-3-carboxamide trifluoroacetate	20	448	MeOD; 7.40(s, 1H), 7.35(dd, 1H), 7.27(dd, 1H), 7.20(s, 1H), 6.93(m, 1H), 4.42(dd, 2H), 4.01(m, 3H), 3.83 (m, 2H), 3.65(dd, 2H), 3.37(q, 4H), 2.44(m, 1H), 2.18(m, 1H), 1.40(t, 6H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide	21	389	1.22 (dd, 1H, J1=12.38 Hz, J2=2.53 Hz), 1.57 (d, 1H, J=13.14 Hz), 1.78 (brt, 2H), 1.95 (brs, 1H), 2.60 (q, 1H, J=11.37), 2.78 (q, 1H, J=10.61 Hz), 3.09 (m, 1H), 3.25 (m, 3H), 3.77 (s, 3H), 6.87 (d, 2H, J=8.59 Hz), 7.44 (d, 2H, J=8.84 Hz), 7.58 (s, 1H), 8.24 (brs, 1H), 8.30 (brt, 1H), 8.57 (brs, 1H), 10.92 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	22	361		III

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-pyrrolidin-3-yl]thiophene-3-carboxamide	23	361		III
2-[(aminocarbonyl)amino]-N-[2-(dimethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	24	363	MeOD; 7.37(d, 2H), 7.35(s, 1H), 6.80(d, 2H), 3.69(s, 3H), 3.64(m, 2H), 3.29(m, 2H), 2.91(s, 6H)	III
2-[(aminocarbonyl)amino]-N-[2-(diethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	25	391		III
2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride	26	389	δ 10.9, s, 1H; δ 9.58, br s, 1H; δ 9.29, br s, 1H; δ 8.39, d, 1H; δ 7.82, s, 1H; δ 7.48, d, 2H; δ 6.96, d, 2H; δ 4.38, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.20, m, 2H; δ 3.07, m, 1H; δ 1.98, m, 1H; δ 1.84, m, 4H; δ 1.59, m, 1H	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide	27	375	1.52 (m, 2H), 1.76 (bra, 1H), 1.89 (bra, 1H), 2.61 (m, 2H), 2.99 (t, 1H), 3.16 (m, 1H), 3.76 (s, 3H), 3.95 (bra, 1H), 6.97 (d, 2H), 7.46 (d, 2H), 7.61 (s, 1H), 7.89 (d, 1H), 10.90 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(piperidin-4-ylmethyl)thiophene-3-carboxamide	28	389	1.06 (m, 2H), 1.62 (d, 3H, J=10.11 Hz), 2.95 (d, 2H, J=12.13 Hz), 3.11 (t, 2H, J=5.88 Hz), 3.76 (s, 3H), 6.90 (d, 1H, J=8.59 Hz), 6.98 (d, 2H, J=8.59 Hz), 7.44 (d, 2H, J=8.59 Hz), 7.61 (s, 1H), 8.14 (t, 1H, J=5.43 Hz), 10.99 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyrrolidin-3-ylthiophene-3-carboxamide	29	361	2.02 (brt, 2H, J=5.81 Hz), 2.22 (dd, 2H, J1=13.52 Hz, J2=6.69 Hz), 3.21 (dd, 1H, J1=13.77 Hz, J2=6.95 Hz), 3.66 (bra, 1H), 3.76 (s, 3H), 3.86 (bra, 1H), 6.96 (brm, 2H), 7.28 (bra, 1H), 7.50 (d, 2H, J=8.84 Hz), 8.16 (bra, 1H), 10.31 (s, 1H)	III
2-[(aminocarbonyl)amino]-N-(1-ethylpiperidin-3-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride	30	403	11.0(s, 1H), 7.80(d, 1H), 7.65(s, 1H), 7.45(d, 2H), 6.95(d, 2H), 6.90(br s, 2H), 3.90(m, 1H), 3.75(s, 3H), 2.85(dd, 2H), 2.30(m, 2H), 1.80(m, 3H), 1.70(m, 1H), 1.50(m, 1H), 13.0(m, 1H), 1.0(t, 3H)	III

2-[(aminocarbonyl)amino]-N-[(3S)-1-ethylazepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride	31	417	11.0(s, 1H), 7.75(d, 1H), 7.65(s, 1H), 7.45(d, 2H), 6.95(d, 2H), 6.90(br s, 2H), 4.05(m, 1H), 3.75(s, 3H), 2.75(m, 1H), 2.40-2.70(m, 5H), 1.85(m, 1H), 1.40-1.75(m, 5H), 0.95(t, 3H)	III
2-[(aminocarbonyl)amino]-5-(3-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	32	361		III
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	33	361		III
2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	34	375		III
tert-butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)pyrrolidine-1-carboxylate	35	461		III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxamide	36	375		III
2-[(aminocarbonyl)amino]-N-(1-benzylpiperidin-4-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	37	465	1.76 (m, 2H), 2.08 (d, 2H, J=13.39 Hz), 3.10 (m, 2H), 3.43 (d, 2H, J=11.82 Hz), 3.76 (s, 3H), 3.95 (m, 1H), 4.31 (d, 2H, J=4.65 Hz), 6.97 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.58 Hz), 7.49 (bra, 5H, J=2.27 Hz), 7.81 (s, 1H), 8.05 (d, 1H, J=8.82 Hz), 9.85 (bra, 1H), 10.89 (s, 1H)	III
tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	38	475	1.39 (s, 9H), 1.46-1.87 (bm, 4H), 2.72 (t, 2H), 3.16 (s, 2H), 3.77 (s, 3H), 6.96 (d, 2H), 7.45 (d, 2H), 7.62 (s, 1H), 7.85 (bra, 1H), 8.77 (d, 1H), 10.95 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	39	494		III
2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	40	451		III

2-[(aminocarbonyl)amino]-N-azetidin-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide	41	347		III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(2S)-pyrrolidin-2-ylmethyl]thiophene-3-carboxamide	42	375	1.71 (m, 1H), 1.92 (m, 2H), 2.04 (m, 1H), 3.33-3.11 (m, 2H), 3.62-3.45 (m, 2H), 3.76 (s, 3H), 6.97 (d, 2H, J=8.84 Hz), 7.45 (d, 2H, J=8.59 Hz), 7.52 (s, 1H), 7.94 (s, 1H), 8.47 (t, 1H, J=5.81 Hz), 8.52 (brs, 1H), 9.15 (brs, 1H), 10.79 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyridin-4-ylthiophene-3-carboxamide	43	389	3.78 (s, 3H), 7.01 (d, 2H), 7.52 (d, 2H), 7.79 (s, 1H), 8.15 (d, 2H), 8.70 (brs, 2H), 10.62 (s, 1H), 10.88 (brs, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide	44	404	2.06 (m, 4H), 2.34 (brs, 2H), 2.42 (m, 2H), 2.67 (m, 4H), 3.76 (s, 3H), 6.97 (d, 2H, J=8.84 Hz), 7.44 (d, 2H, J=8.59 Hz), 7.55 (s, 1H), 8.10 (t, 1H, J=5.68 Hz), 10.95 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperidin-1-ylethyl)thiophene-3-carboxamide	45	403	1.37 (s, 2H), 1.48 (s, 4H), 2.37 (brs, 4H), 2.42 (t, 2H), 3.76 (s, 3H), 6.94 (brs, 1H), 6.97 (d, 2H), 7.44 (d, 2H), 7.56 (t, 2H), 8.11 (t, 1H), 10.96 (s, 1H)	III
2-[(aminocarbonyl)amino]-N-1-azabicyclo[2.2.2]oct-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide	46	401		III
2-[(aminocarbonyl)amino]-N-(2-hydroxyethyl)-5-(4-hydroxyphenyl)thiophene-3-carboxamide	48	322	3.06(t,1H), 3.5(m,2H), 6.54(ba,1H), 6.78-6.97(m,4H), 7.33(m,2H),7.49(s,1H), 8.34(m,1H), 9.56(s,1H), 10.94(s,1H)	III
2-[(aminocarbonyl)amino]-N-(trans-4-hydroxycyclohexyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	49	390	1.10-1.45 (dq, 4H), 1.85 (t, 4H), 3.40 (brs, 1H), 3.71 (brm, 1H), 3.76 (s, 3H), 4.56 (brs, 1H), 6.90 (brs, 1H), 6.96 (d, 2H), 7.45 (d, 2H), 7.62 (s, 1H), 7.81 (d, 1H), 11.03 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	50	383	3.17 (t, 2H, J=6.44 Hz), 3.84 (m, 2H), 6.77 (d, 2H, J=8.59 Hz), 7.31 (d, 2H, J=8.59 Hz), 7.45 (s, 1H), 7.97 (d, 2H, J=6.32 Hz), 8.27 (s, 1H), 8.83 (d, 2H, J=6.06 Hz), 10.79 (s, 1H)	III

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2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide	52	525	1.34-1.58 (m, 2H), 1.75 (t, 2H, J=14.02 Hz), 1.98 (brs, 1H), 2.01 (d, 1H), 2.80 (m, 3H), 3.48 (d, 2H, J=8.59 Hz), 3.73 (s, 8H), 3.75 (s, 3H), 6.63 (dd, 2H, J1=8.34 Hz, J2=4.80 Hz), 6.90 (brs, 1H), 6.95 (d, 2H, J=8.59 Hz), 7.21 (t, 2H), 7.45 (d, 2H, J=8.84 Hz), 7.46 (s, 1H), 7.86 (d, 1H, J=7.58 Hz), 11.00 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	54	397	3.12 (t, 2H), 3.62 (t, 2H), 3.76 (s, 3H), 6.97 (d, 2H), 7.42 (d, 2H), 7.49 (s, 1H), 7.85 (d, 2H), 8.28 (s, 1H), 8.78 (d, 2H), 10.84 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide	55	383	3.17 (t, 2H, J=6.44 Hz), 3.64 (m, 2H), 6.77 (d, 2H, J=8.59 Hz), 7.31 (d, 2H, J=8.59 Hz), 7.45 (s, 1H), 7.97 (d, 2H, J=6.32 Hz), 8.27 (s, 1H), 6.83 (d, 2H, J=6.06 Hz), 10.79 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide	56	397	2.99 (t, 2H), 3.55 (m, 2H), 3.76 (s, 3H), 6.97 (d, 2H), 7.42 (d, 2H), 7.50 (s, 1H), 7.76 (m, 1H), 8.16 (d, 1H), 8.25 (s, 1H), 8.65 (s, 1H), 8.69 (s, 1H), 10.85 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)thiophene-3-carboxamide	58	431	1.44 (s, 12H), 1.63 (t, 2H), 1.95 (d, 2H), 3.76 (s, 3H), 4.34 (brs, 1H), 6.96 (d, 2H), 7.45 (d, 2H), 7.87 (s, 1H), 8.12 (m, 2H), 9.06 (bd, 1H), 10.92 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(2-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	59	376		III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(tetrahydrofuran-2-ylmethyl)thiophene-3-carboxamide	60	378	1.52(m,1H), 1.77(m,3H), 3.25(m,2H), 3.72(m,1H), 3.71(s,3H), 3.93(m,2H), 6.91(bd,4H,J=8.84Hz), 7.39(d,2H,J=8.59Hz), 7.59(s,1H), 8.17(bs,1H), 10.91(s,1H)	III
tert-butyl (3R)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	62	475	1.38 (s, 9H), 1.47-1.99 (brm, 6H), 3.58 (brm, 2H), 3.74 (brm, 1H), 3.76 (s, 3H), 6.96 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.84 Hz), 7.52 (s, 1H), 7.85 (brs, 1H), 8.77 (d, 1H, J=7.58 Hz), 10.96 (s, 1H	III

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-3-ylmethyl)thiophene-3-carboxamide	83	383	3.76 (s, 3H), 4.48 (d, 2H), 6.96 (d, 2H), 7.36 (dd, 1H), 7.44 (d, 2H), 7.61 (s, 1H), 7.72 (dt, 1H), 8.48 (bdd, 1H), 8.58 (bd, 1H), 8.77 (t, 1H)	III
tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azetidine-1-carboxylate	84	447	1.39 (s, 9H), 3.77 (s, 3H), 3.88 (m, 2H), 4.13 (t, 2H, J=7.83 Hz), 4.61 (m, 1H), 6.97 (d, 2H, J=8.84 Hz), 7.45 (d, 2H, J=8.59 Hz), 7.60 (s, 1H), 8.57 (d, 1H, J=8.82 Hz), 10.82 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-4-ylmethyl)thiophene-3-carboxamide	85	383		III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(3-methoxypropyl)thiophene-3-carboxamide	87	364	1.76 (m, 2H), 3.23 (s, 3H), 3.30 (t, 2H), 3.37 (t, 2H), 3.76 (s, 3H), 6.96 (d, 2H), 7.44 (d, 2H), 7.57 (s, 1H), 8.15 (bra, 1H), 10.97 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide	88	402		III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide	89	388	3.76 (s, 3H), 4.62 (d, 2H), 6.96 (d, 1H), 6.96 (d, 2H), 7.03 (d, 1H), 7.39 (d, 1H), 7.43 (d, 2H), 7.80 (s, 1H), 8.79 (t, 1H), 10.92 (s, 1H)	III
N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]urea	70	375	7.50 d J=8.8 Hz 2H, 7.09 s 1H, 6.95 d J=8.8 Hz 2H, 3.86 s 3H, 1.23-1.35 m 8H.	III
2-[(aminocarbonyl)amino]-N-(2-methoxyethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	71	350	3.27 (s, 3H), 3.37-3.51 (m, 4H), 3.76 (s, 3H), 6.97 (d, 2H), 7.44 (d, 2H), 7.61 (s, 1H), 8.15-8.26 (m, 1H), 10.95 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide	72	374	4.61 (d, 2H, J=5.81 Hz), 6.77 (d, 2H, J=8.59 Hz), 6.96 (dd, 2H, J1=5.05 Hz, J2=3.54 Hz), 7.02 (d, 1H, J=3.03 Hz), 7.32 (d, 2H, J=8.34 Hz), 7.38 (d, 1H, J=5.05 Hz), 7.53 (s, 1H), 8.77 (t, 1H, J=5.81 Hz), 9.53 (s, 1H), 10.69 (s, 1H)	III

2-[(aminocarbonyl)amino]-N-[2-[(2-furylmethyl)thio]ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	74	432	2.61 (t, 2H), 2.66 (t, 2H), 3.75 (s, 3H), 3.81 (d, 2H), 6.29 (d, 1H, J=3.03 Hz), 6.36 (dd, 1H, J1=3.03 Hz, J2=1.77 Hz), 6.97 (d, 2H, J=8.84 Hz), 7.44 (d, 2H, J=8.84 Hz), 7.55 (s, 1H), 7.57 (bra, 1H), 8.31 (t, 1H, J=5.68 Hz), 9.10 (t, 1H, J=4.93 Hz), 10.92 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide	75	388	3.50(m,2H), 3.60(m,2H), 6.54(ba,1H), 6.76-7.34(m,7H), 7.49(s,1H), 8.34(m,1H), 9.58(s,1H), 10.94(s,1H)	III
N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-[3-[2-(diethylamino)ethoxy]phenyl]-2-thienyl)urea trifluoroacetate	76	480	MeOD; 7.24(dd, 1H), 7.16(dd, 1H), 7.08(s, 1H), 7.06(s, 1H), 6.83(dd, 1H), 4.34(m, 2H), 4.30(dd, 2H), 3.53(dd, 2H), 3.32(m, 1H), 3.27(q, 4H), 3.04(m, 2H), 1.99(m, 2H), 1.50(m, 2H), 1.28(t, 6H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide	77	389	1.22 (dd, 1H, J1=12.38 Hz, J2=2.53 Hz), 1.57 (d, 1H, J=13.14 Hz), 1.76 (brt, 2H), 1.96 (bra, 1H), 2.60 (q, 1H, J=11.37), 2.78 (q, 1H, J=10.61 Hz), 3.09 (m, 1H), 3.26 (m, 3H), 3.77 (s, 3H), 6.97 (d, 2H, J=8.59 Hz), 7.44 (d, 2H, J=8.84 Hz), 7.58 (s, 1H), 8.24 (bra, 1H), 8.30 (brt, 1H), 8.57 (bra, 1H), 10.92 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1,2,3,4-tetrahydroquinolin-3-yl)thiophene-3-carboxamide	78	423		III
2-[(aminocarbonyl)amino]-N-(1,3-benzodioxol-5-ylmethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	79	426	3.76 (s, 3H), 4.36 (d, 2H), 5.97 (s, 2H), 6.81 (d, 1H), 6.89 (d, 1H), 6.98 (d, 2H), 7.44 (d, 2H), 7.62 (s, 1H), 8.64 (t, 1H), 10.94 (s, 1H)	III
2-[(aminocarbonyl)amino]-N-(3-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	80	412	3.74(s,3H), 3.76(s,3H), 4.44(d,2H,J=5.56Hz), 6.82(m,1H), 6.91(m,2H), 6.98(d,2H,J=8.59Hz), 7.25(t, 2H, J=7.83), 7.48(d,2H,J=8.59Hz),7.68(s,1H), 8.71(s,1H), 10.95(s,1H)	III

2-[(aminocarbonyl)amino]-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	81	458	3.73(s,3H), 3.74(s,3H), 3.77(s,3H), 4.40(d,2H,J=5.58Hz), 6.92(m,7H), 7.45(d,2H,J=8.84Hz), 7.86(s,1H), 8.84(bs,1H), 10.97(s,1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(5-methyl-2-furyl)methyl]thiophene-3-carboxamide	84	388	2.22 (s, 3H), 3.76 (s, 3H), 4.36 (d, 2H), 5.99 (s, 1H), 6.14 (s, 1H), 6.96 (d, 2H), 7.43 (d, 2H), 7.84 (s, 1H), 8.57 (t, 1H), 10.93 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-2-ylmethyl)thiophene-3-carboxamide	85	383	3.77 (s, 3H), 4.69 (d, 2H), 6.98 (d, 2H), 7.46 (d, 2H), 7.65 (t, 1H), 7.73 (t, 1H), 7.87 (s, 1H), 8.20 (t, 1H), 8.69 (d, 1H), 8.96 (t, 1H), 10.76 (s, 1H)	III
2-[(aminocarbonyl)amino]-N-(4-fluorobenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	88	400		III
tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	88	475		III
2-[(aminocarbonyl)amino]-N-(2-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	89	412	3.78(s,3H), 3.83(s,3H), 4.45(bd,2h,J=5.58Hz), 6.97(m,5H(, 7.23(m,2H), 7.47(d,2H,J=8.84), 7.71(s,1H), 8.55(bt,1H), 10.97(s,1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-phenoxyethyl)thiophene-3-carboxamide	90	412	3.58-3.7 (m, 2H), 3.76 (s, 3H), 4.11 (t, 2H), 6.85-7.05 (m, 5H); 7.28 (t, 2H), 7.44 (d, 2H), 7.81 (s, 1H), 8.36 (brs, 1H), 10.93 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-2-ylethyl)thiophene-3-carboxamide	93	397	3.00 (t, 2H, J=7.45 Hz), 3.61 (m, 2H), 3.76 (s, 3H), 6.97 (d, 2H, J=8.84 Hz), 7.22 (dd, 1H, J1=6.95 Hz, J2=5.18 Hz), 7.27 (d, 1H, J=7.83 Hz), 7.43 (d, 2H, J=8.59 Hz), 7.54 (s, 1H), 7.70 (dt, 1H, J1=7.58 Hz, J2=1.77 Hz), 8.27 (t, 1H, J=5.68 Hz), 8.51 (d, 1H, J=4.55 Hz), 10.97 (s, 1H)	III
tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	94	475		III

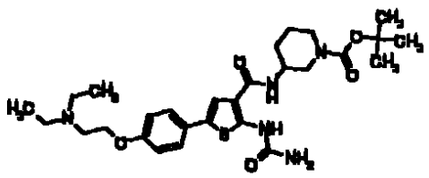
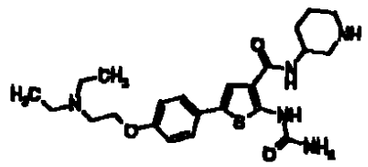
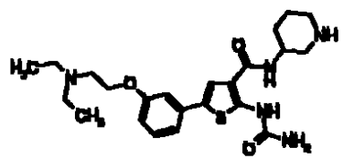
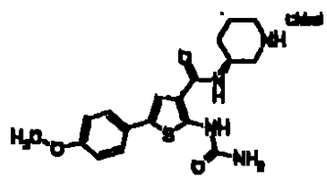
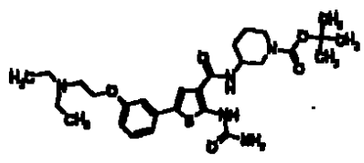
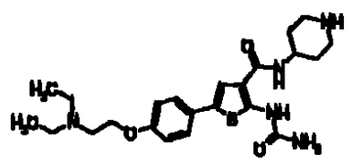
2-[(aminocarbonyl)amino]-N-(4-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	93	412	3.72 (s, 3H), 3.76 (s, 3H), 4.39 (d, 2H), 6.89 (d, 2H), 6.96 (d, 2H), 7.25 (d, 2H), 7.44 (d, 2H), 7.83 (s, 1H), 8.64 (t, 1H), 10.95 (s, 1H)	III
2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide trifluoroacetate	110	480	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.60(dd, 2H), 3.50(m, 1H), 3.30(m, 5H), 2.95(dd, 2H), 2.10(dd, 2H), 1.90(m, 2H), 1.35(t, 6H)	IV
2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide trifluoroacetate	111	480	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.60(dd, 2H), 3.50(m, 1H), 3.30(m, 5H), 2.95(dd, 2H), 2.10(dd, 2H), 1.90(m, 2H), 1.35(t, 6H)	IV
tert-butyl (3S)-3-{[(2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	112	580	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 3.80-3.90(m, 3H), 3.60(dd, 2H), 3.30(m, 4H), 2.95(m, 2H), 1.90(dd, 2H), 1.55(m, 2H), 1.45(s, 9H), 1.35(t, 6H)	IV
2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxamide hydrochloride	113	474	10.85(s, 1H), 9.50(br s, 1H), 9.10(br s, 1H), 8.95(br s, 1H), 8.20(d, 1H), 7.65(s, 1H), 7.50(d, 2H), 7.05(d, 2H), 6.95, (br s, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.50(dd,2H), 3.10-3.40(m, 8H), 2.00(m, 1H), 1.80(m, 4H), 1.55(m, 1H), 1.25(t, 6H)	IV
tert-butyl (3R)-3-{[(2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	114	580	MeOD; 7.45(d, 2H), 7.35(s, 1H), 6.90(d, 2H), 4.25(dd, 2H), 3.80-3.90(m, 3H), 3.50(dd, 2H), 3.20(m, 5H), 2.85(s, 1H), 1.80(dd, 2H), 1.45(m, 2H), 1.35(s, 9H), 1.25(t, 6H)	IV
N-[3-[[(3S)-3-aminoazepan-1-yl]carbonyl]-5-(4-methoxyphenyl)-2-thienyl]urea hydrochloride	115	389	9.85 (s, 1H), 8.25 (s, 3H), 7.50 (d, 2H), 7.10(s, 1H), 6.90(d, 2H), 6.75 (br s, 2H), 4.00 (m, 1H), 3.80(s, 3H), 3.40 (m, 4H), 2.0 (m, 1H), 1.00-1.80 (m, 5H)	IV
2-{[[(2,5-dimethoxyphenyl)amino]carbonyl}amino)-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxamide	116	511	11.28 s 1H, 9.85 bs 1H, 9.08 bs 1H, 8.43 s 1H, 7.90 s 1H, 7.46 d J = 8.7 Hz 2H, 6.93 d J = 8.8 Hz 2H, 6.85 d J = 8.8 Hz 1H, 6.43 - 6.47 m 1H, 4.35 bs 1H, 3.78 s 3H, 7.73 s 3H, 3.54 s 3H, 3.24 - 3.45 m 2H, 2.81 bs 2H, 2.44 bs 4H.	V

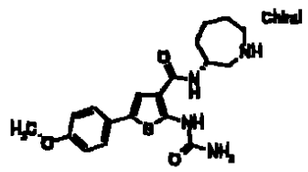
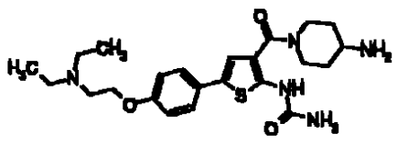
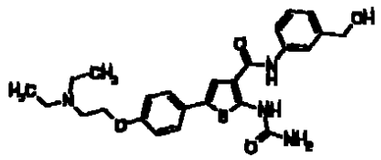
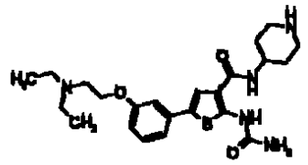
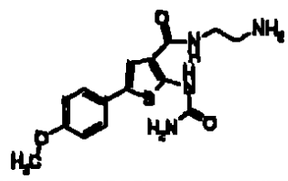
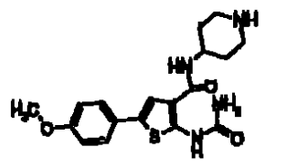
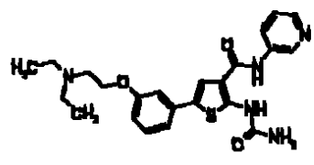
5-[4-[2-(diethylamino)ethoxy]phenyl]-2-[[(pyrazin-2-ylamino)carbonyl]amino]-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	120	524	1.21 (t, 6H), 2.00 (m, 1H), 2.20 (m, 1H), 3.18 (m, 4H), 3.43 (m, 6H), 4.31 (t, 2H), 4.53 (m, 1H), 7.05 (d, 2H), 7.52 (d, 2H), 7.70 (s, 1H), 8.30 (m, 3H), 8.78 (s, 1H), 8.85 (s, 1H), 8.96 (s, 1H), 9.32 (s, 1H), 10.90 (s, 1H)	VI
5-[3-[2-(diethylamino)ethoxy]phenyl]-2-[[(pyrazin-2-ylamino)carbonyl]amino]-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide hydrochloride	121	524	1.25 (t, 6H), 2.02 (m, 1H), 2.20 (m, 1H), 3.22 (m, 4H), 3.43 (m, 6H), 4.34 (t, 2H), 4.53 (m, 1H), 6.92 (d, 1H), 7.12 (s, 1H), 7.28 (d, 1H), 7.39 (dxd, 1H), 7.84 (s, 1H), 8.32 (m, 3H), 8.78 (s, 1H), 8.85 (s, 1H), 8.96 (s, 1H), 9.30 (s, 1H), 10.92 (s, 1H)	VI
5-[3-[2-(diethylamino)ethoxy]phenyl]-N-piperidin-4-yl-2-[[(pyrazin-2-ylamino)carbonyl]amino]thiophene-3-carboxamide	122	538	): 0.95 (t, 6H), 1.52 (m, 2H), 1.82 (m, 4H), 2.52 (m, 4H), 2.78 (m, 4H), 3.00 (m, 12H), 3.18 (t, 2H), 4.05 (t, 2H), 6.68 (bs, 1H), 6.80 (d, 1H), 7.10 (m, 2H), 7.28 (m, 2H), 7.82 (s, 1H), 8.22 (s, 1H), 8.28 (s, 1H), 9.00 (s, 1H)	VI
N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)-2-[[(pyrazin-2-ylamino)carbonyl]amino]thiophene-3-carboxamide hydrochloride	123	487	δ 12.8, br s, 1H; δ 10.9, s, 1H; δ 9.55, br s, 1H; δ 9.24, br s, 1H; δ 8.88, s, 1H; δ 8.49, d, 1H; δ 8.35, dd, 1H; δ 8.29, d, 1H; δ 7.92, s, 1H; δ 7.54, d, 2H; δ 6.99, d, 2H; δ 4.42, m, 1H; δ 3.33, m, 1H; δ 3.23, m, 2H; δ 3.10, m, 1H; δ 2.02, m, 1H; δ 1.85, m, 4H; δ 1.62, m, 1H	VI
5-[3-[2-(diethylamino)ethoxy]phenyl]-N-piperidin-3-yl-2-[[(pyrazin-2-ylamino)carbonyl]amino]thiophene-3-carboxamide hydrochloride	124	538	0.95 (t, 6H), 1.52 (m, 2H), 1.82 (m, 4H), 2.52 (m, 4H), 2.78 (m, 4H), 3.00 (m, 12H), 3.18 (t, 2H), 4.05 (t, 2H), 6.68 (bs, 1H), 6.80 (d, 1H), 7.10 (m, 2H), 7.28 (m, 2H), 7.82 (s, 1H), 8.22 (s, 1H), 8.28 (s, 1H), 9.00 (s, 1H)	VI
N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-[[(pyrazin-2-ylamino)carbonyl]amino]thiophene-3-carboxamide	125	413	8.53 s 1H, 8.31-8.33 m 1H, 8.13 d J=2.8 Hz 1H, 7.42 d J=8.8 Hz 2H, 7.38 s 1H, 6.85 d J=8.8 Hz 2H, 3.72 s 3H.	VI
5-[4-[2-(diethylamino)ethoxy]phenyl]-N-piperidin-3-yl-2-[[(pyrazin-2-ylamino)carbonyl]amino]thiophene-3-carboxamide	126	538	0.95 (t, 6H), 1.52 (m, 2H), 1.79 (m, 2H), 2.42 (m, 4H), 2.70 (m, 4H), 3.08 (m, 2H), 3.98 (m, 3H), 6.95 (d, 2H), 7.48 (d, 2H), 7.70 (s, 1H), 8.28 (d, 2H), 8.95 (s, 1H)	VI

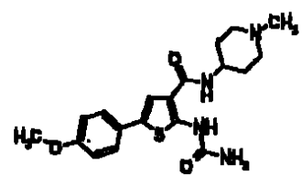
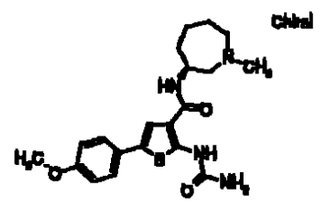
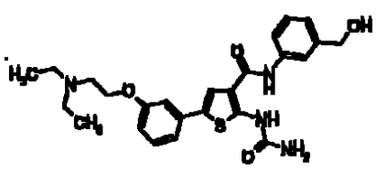
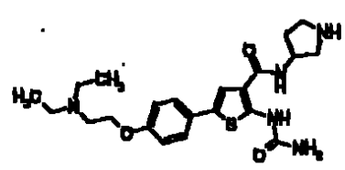
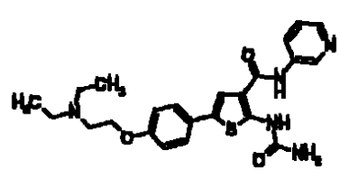
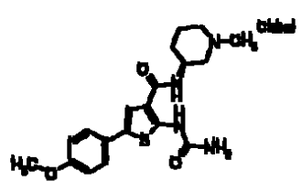
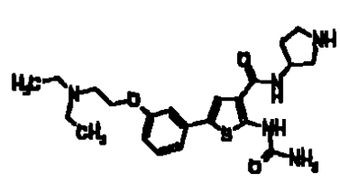
5-(4-methoxyphenyl)-N-piperidin-4-yl-2-[[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	127	453		VI
tert-butyl 3-[[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-[[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	128	638	1.21 (t, 6H), 1.32 (s, 9H), 1.75 (m, 1H), 1.92 (m, 1H), 2.85 (m, 1H), 3.20 (m, 4H), 3.50 (t, 2H), 3.80 (m, 2H), 4.35(t,2H), 6.90 (d, 1H), 7.15 (s, 1H) 7.25 (d, 1H), 7.38 (dxd, 1H), 7.76 (s, 1H), 7.98 (bs, 1H), 8.30 (d, 2H), 8.90 (s, 1H), 9.25 (bs, 1H),10.92 (s, 1H)	VI
5-(4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-[[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	129	538	0.95 (t, 6H), 1.52 (m, 2H), 1.78 (m, 2H), 2.42 (m, 4H), 2.70 (m, 4H), 3.08 (m, 2H), 3.98 (m, 3H), 6.95 (d, 2H), 7.48 (d, 2H), 7.70 (s, 1H), 8.28 (d, 2H), 8.95 (s, 1H)	VI
5-(4-methoxyphenyl)-2-[[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	130	439		VI
N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea	131	483	8.47 s 1H, 8.14-8.25 m 2H, 7.43 d J=8.8 Hz 2H, 7.06 s 1H, 7.85 d J=8.8 Hz 2H, 3.90 bs 2H, 3.79 t J=8.0 Hz 2H, 3.72 s 3H, 3.40 bs 2H, 2.10 bs 2H.	VI
N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea	132	439	11.97 bs 1H, 10.72 s 1H, 8.79 s 1H, 8.22-8.26 m 2H, 7.50 d J=8.8 Hz 2H, 8.04 bs 2H, 7.31 s 1H, 7.20-7.25 m 2H, 7.08 d J=8.3 Hz 1H, 7.00 t J=7.2 Hz 1H, 6.92 d J=8.8 Hz 2H3.72 s 3H, 2.11-2.19 m 1H, 3.80 bs 2H, 3.64 bs 2H.	VI
tert-butyl 4-[[(5-(4-methoxyphenyl)-2-[[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate	133	553		VI
tert-butyl 3-[[(5-{4-[2-(diethylamino)ethoxy]phenyl}-2-[[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate	134	638	1.18 (t, 6H), 1.32 (s, 9H), 1.72 (m, 1H), 1.90 (m, 1H), 2.85 (m, 1H), 3.21 (m, 4H), 3.50 (t, 2H), 3.80 (m, 2H), 4.30 (t,2H), 7.05 (d, 2H), 7.52 (d, 2H), 7.76 (s, 1H), 7.92 (bs, 1H), 8.30 (d, 2H), 8.90 (s, 1H), 9.25 (bs, 1H),10.90 (s, 1H)	VI

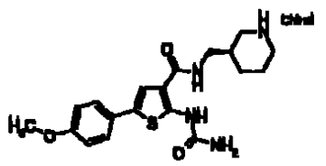
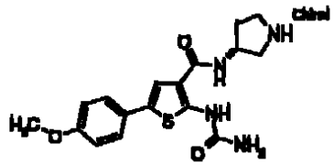
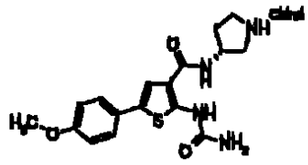
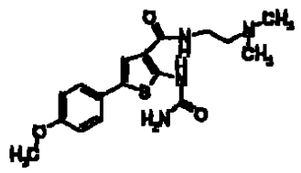
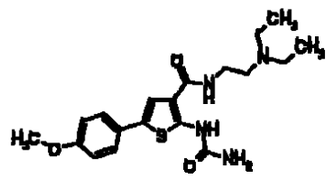
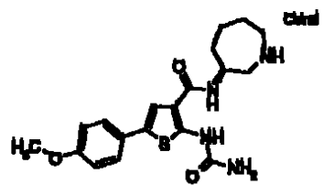
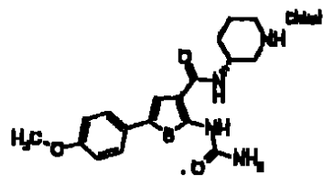
5-[4-(2-diethylamino-ethoxy)-phenyl]-2-(3-hydroxy-urea)-thiophene-3-carboxylic acid-(S)-piperidin-3-ylamide	138	476	δ 1.17 - 1.40 (m, 8 H) 1.54 - 1.81 (m, 2 H) 1.84 - 2.07 (m, 2 H) 2.76 - 2.99 (m, 2 H) 3.05 - 3.25 (m, 4 H) 3.41 - 3.81 (m, 4 H) 3.73 - 3.88 (m, 1 H) 4.29 - 4.42 (m, 1 H) 4.40 - 4.64 (m, 1 H) 5.86 (s, 1 H) 7.07 (d, J=8.48 Hz, 2 H) 7.55 (d, J=8.48 Hz, 2 H) 7.82 (s, 1 H) 9.44 (s, 1 H) 9.85 (s, 1 H);	VII
2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(3-methoxyphenyl)thiophene-3-carboxamide	137	389	10.90 (s, 1H), 9.21 (s, 1H), 9.01 (s, 1H), 8.29 (d, 1H), 7.93 (s, 1H), 7.29 (t, 1H), 7.11 (d, 2H), 7.03 (s, 1H), 8.83 (d, 1H), 4.33 (s, 1H), 3.81 (s, 3H), 3.20 (m, 4H), 2.00 (m, 1H), 1.84 (m, 4H), 1.58 (m, 1H).	VIII
2-[(aminocarbonyl)amino]-5-(2-hydroxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	138	361	δ 10.85 (s, 1H), 10.13 (s, 1H), 9.29 (d, 2H), 8.31 (d, 1H), 7.92 (s, 1H), 7.63 (dd, 1H), 7.05 (td, 1H), 6.94 (dd, 1H), 6.82 (td, 1H), 6.91 (brs, 2H), 4.21 (brs, 1H), 3.26 (dd, 2H), 2.89 (m, 2H), 1.88-1.618 (m, 4H).	VIII
2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	139	375	10.94 (s, 1H), 9.41 (s, 1H), 9.19 (s, 1H), 8.47 (d, 1H), 8.11 (s, 1H), 7.30 (t, 1H), 7.15 (d, 1H), 7.05 (br, 2H), 6.84 (d, 1H), 4.25 (s, 1H), 3.82 (s, 3H), 3.29 (d, 1H), 3.12 (d, 1H), 2.97 (m, 2H), 1.92 (d, 2H), 1.69 (m, 2H).	VIII
2-[(aminocarbonyl)amino]-5-[2-(benzyloxy)phenyl]-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	140	451	δ 10.8 (s, 1H), 8.83 (brs, 2H), 8.04 (d, 1H), 7.79 (s, 1H), 7.63 (d, 1H), 7.55 (d, 2H), 7.38 (t, 2H), 7.31 (t, 1H), 7.23 (t, 1H), 7.20 (t, 1H), 7.02 (t, 1H), 6.95 (m, 2H), 5.28 (s, 2H), 4.15 (m, 1H), 3.24 (m,1H), 2.85 (m, 2H), 1.90-1.58 (m, 5H).	VIII

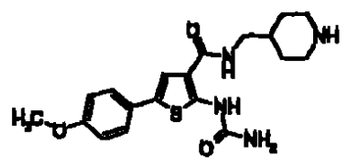
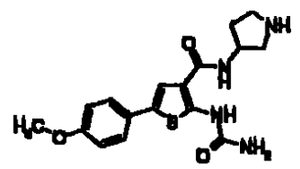
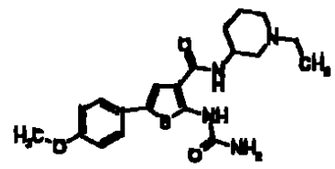
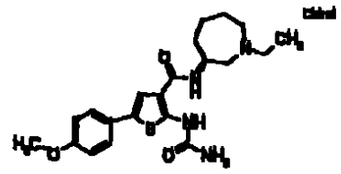
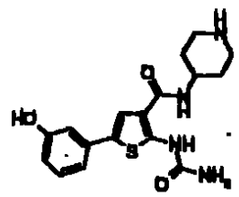
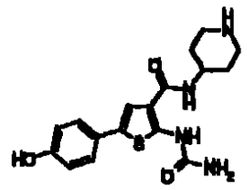
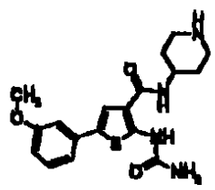
Table 2

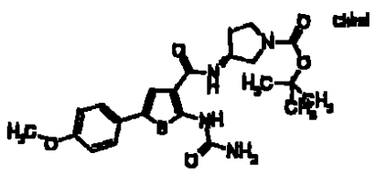
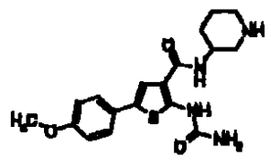
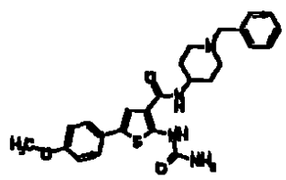
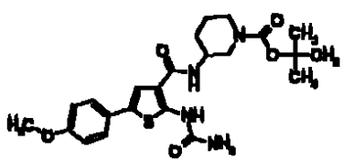
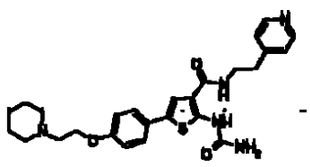
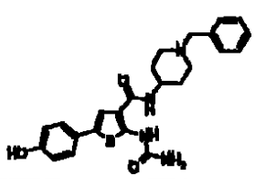
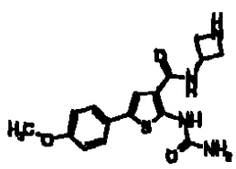
Structure	IUPAC Name	M.W. (g/mol)	Ex.
	tert-butyl 3-{[(2-{(aminocarbonyl)amino}-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	559.7	1
	2-{(aminocarbonyl)amino}-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide trifluoroacetate	459.6	2
	2-{(aminocarbonyl)amino}-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide trifluoroacetate	459.6	3
	2-{(aminocarbonyl)amino}-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	374.5	4
	tert-butyl 3-{[(2-{(aminocarbonyl)amino}-5-{3-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	559.7	5
	2-{(aminocarbonyl)amino}-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide	459.6	6

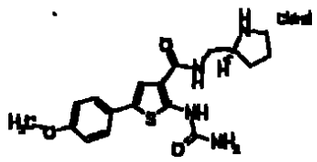
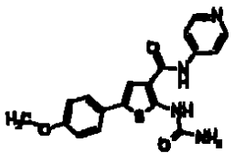
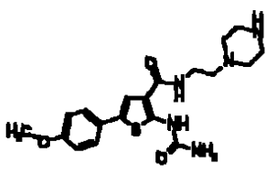
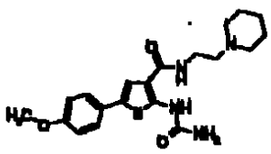
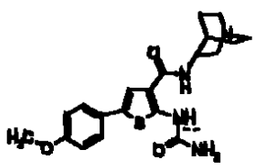
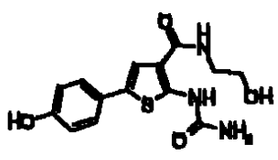
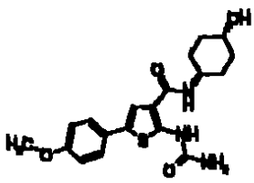
	2-[(aminocarbonyl)amino]-N-[(3R)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	388.5	7
	N-{3-[(4-aminopiperidin-1-yl)carbonyl]-5-{4-[2-(diethylamino)ethoxy]phenyl}-2-thienyl}urea trifluoroacetate	459.6	8
	2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide trifluoroacetate (salt)	482.6	9
	2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide trifluoroacetate	459.6	10
	2-[(aminocarbonyl)amino]-N-(2-aminoethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	334.4	11
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	374.5	12
	2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-pyridin-3-ylthiophene-3-carboxamide trifluoroacetate	453.6	13

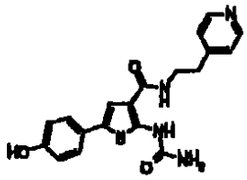
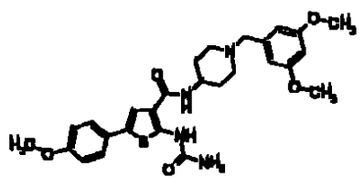
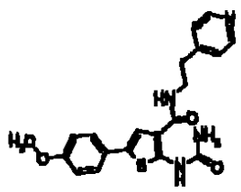
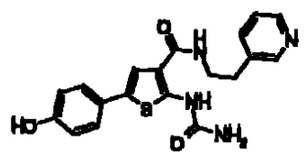
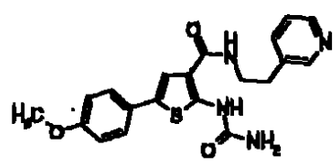
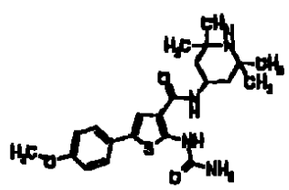
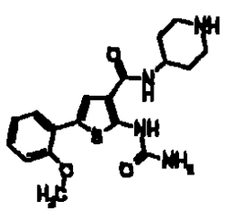
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1-methylpiperidin-4-yl)thiophene-3-carboxamide	388.5	14
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylazepan-3-yl]thiophene-3-carboxamide hydrochloride	402.5	15
	2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide trifluoroacetate (salt)	482.6	16
	2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-pyrrolidin-3-ylthiophene-3-carboxamide trifluoroacetate	445.6	17
	2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-pyridin-3-ylthiophene-3-carboxamide trifluoroacetate	453.6	18
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]thiophene-3-carboxamide hydrochloride	388.5	19
	2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-pyrrolidin-3-ylthiophene-3-carboxamide trifluoroacetate	445.6	20

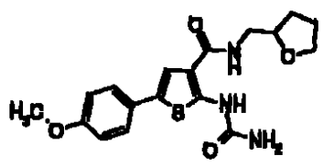
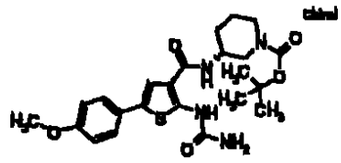
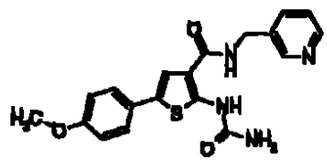
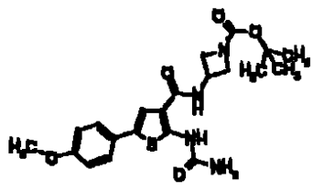
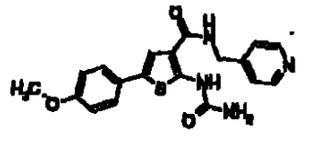
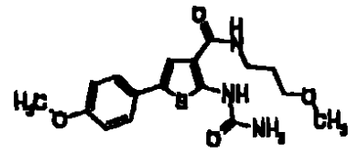
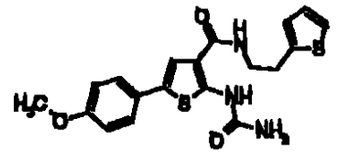
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide	388.5	21
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	360.4	22
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-pyrrolidin-3-yl]thiophene-3-carboxamide	360.4	23
	2-[(aminocarbonyl)amino]-N-[2-(dimethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	362.4	24
	2-[(aminocarbonyl)amino]-N-[2-(diethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	390.5	25
	2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride	388.5	26
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide	374.5	27

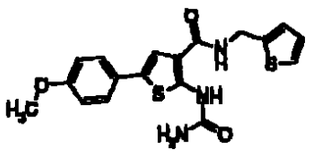
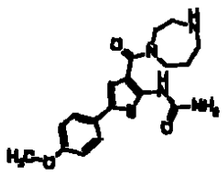
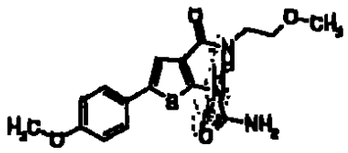
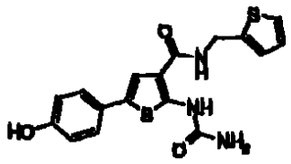
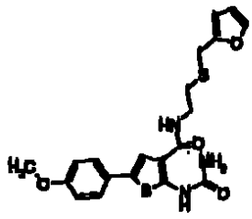
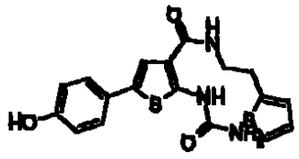
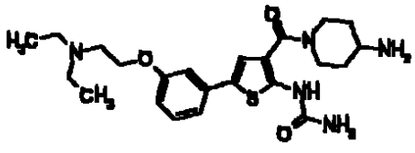
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(piperidin-4-ylmethyl)thiophene-3-carboxamide	388.5	28
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyrrolidin-3-ylthiophene-3-carboxamide	360.4	29
	2-[(aminocarbonyl)amino]-N-(1-ethylpiperidin-3-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride	402.5	30
	2-[(aminocarbonyl)amino]-N-[(3S)-1-ethylazepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride	416.5	31
	2-[(aminocarbonyl)amino]-5-(3-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	360.4	32
	2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	360.4	33
	2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	374.5	34

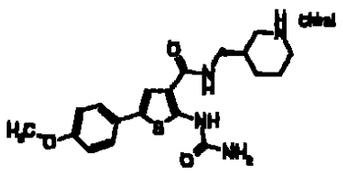
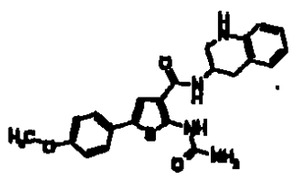
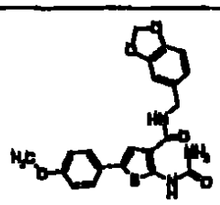
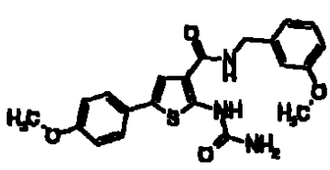
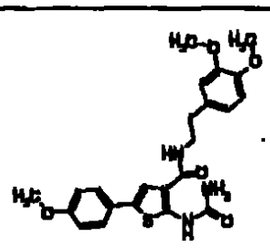
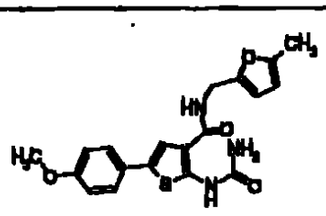
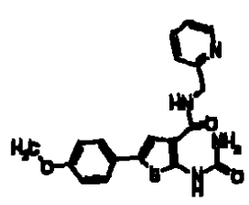
	tert-butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)pyrrolidine-1-carboxylate	460.6	35
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxamide	374.5	36
	2-[(aminocarbonyl)amino]-N-(1-benzylpiperidin-4-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	464.6	37
	tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	474.6	38
	2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	493.6	39
	2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	450.6	40
	2-[(aminocarbonyl)amino]-N-azetidin-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide	346.4	41

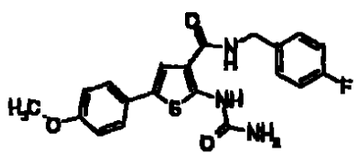
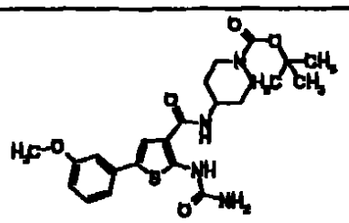
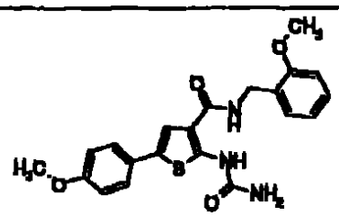
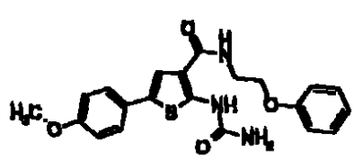
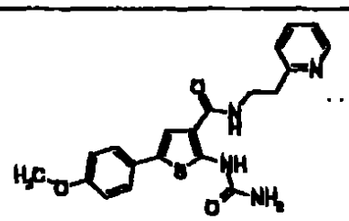
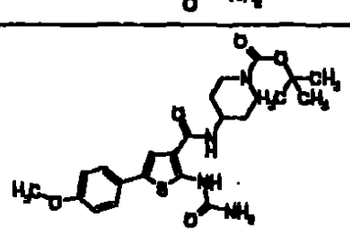
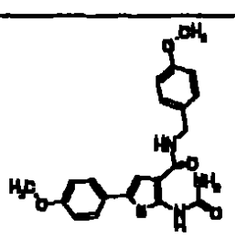
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(2S)-pyrrolidin-2-ylmethyl]thiophene-3-carboxamide	374.5	42
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyridin-4-ylthiophene-3-carboxamide	368.4	43
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide	403.5	44
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperidin-1-ylethyl)thiophene-3-carboxamide	402.5	45
	2-[(aminocarbonyl)amino]-N-1-azabicyclo[2.2.2]oct-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide	400.5	46
	2-[(aminocarbonyl)amino]-N-(2-hydroxyethyl)-5-(4-hydroxyphenyl)thiophene-3-carboxamide	321.4	48
	2-[(aminocarbonyl)amino]-N-(trans-4-hydroxycyclohexyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	389.5	49

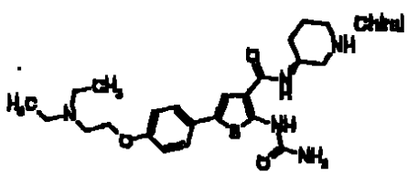
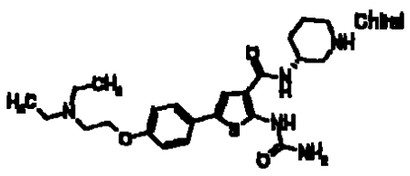
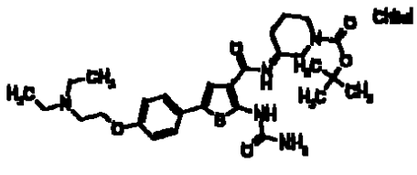
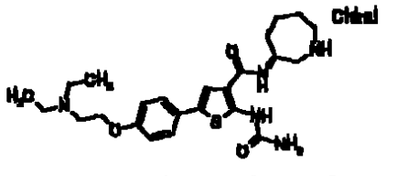
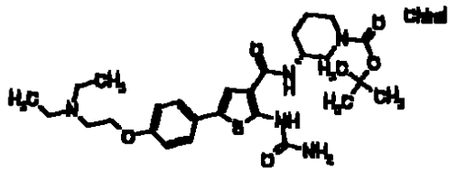
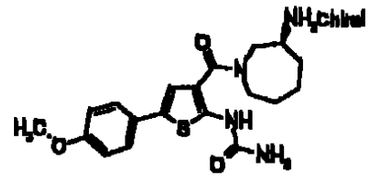
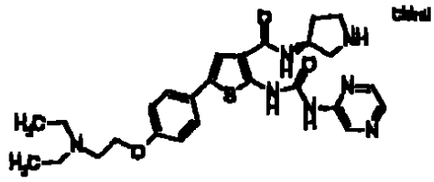
	2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	382.4	50
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide	524.6	52
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide	396.5	54
	2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide	382.4	55
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide	396.5	56
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)thiophene-3-carboxamide	430.6	58
	2-[(aminocarbonyl)amino]-5-(2-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide	374.5	59

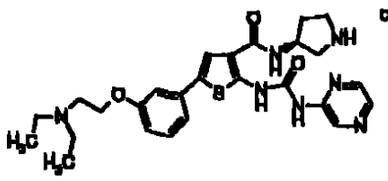
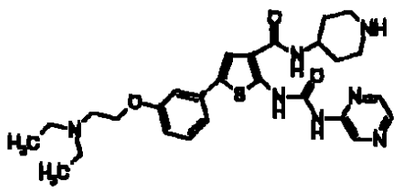
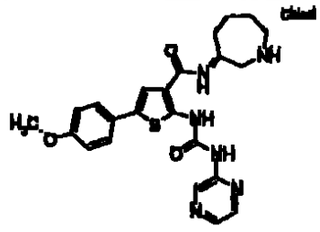
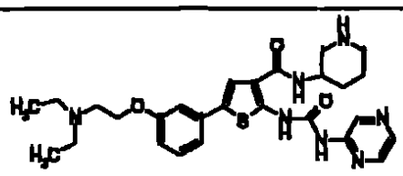
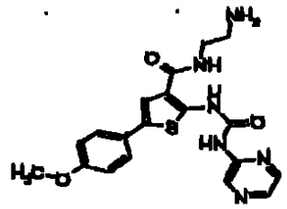
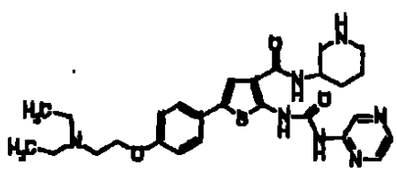
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(tetrahydrofuran-2-ylmethyl)thiophene-3-carboxamide	375.4	60
	tert-butyl (3R)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	474.6	62
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-3-ylmethyl)thiophene-3-carboxamide	382.4	63
	tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azetidine-1-carboxylate	446.5	64
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-4-ylmethyl)thiophene-3-carboxamide	382.4	65
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(3-methoxypropyl)thiophene-3-carboxamide	363.4	67
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide	401.5	68

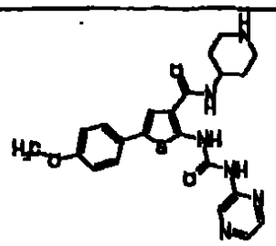
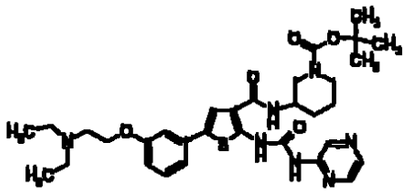
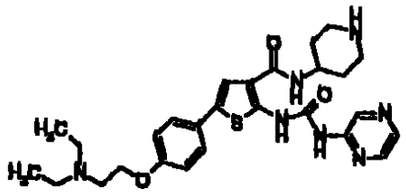
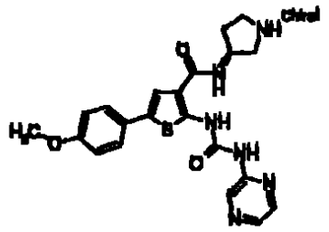
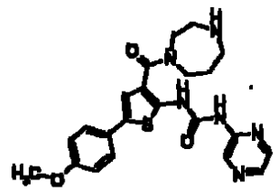
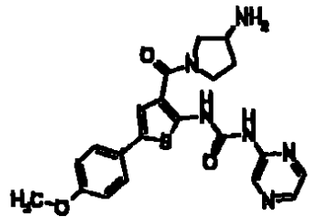
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide	387.5	69
	N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]urea	374.5	70
	2-[(aminocarbonyl)amino]-N-(2-methoxyethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	349.4	71
	2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide	373.5	72
	2-[(aminocarbonyl)amino]-N-[2-[(2-furylmethyl)thio]ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	431.5	74
	2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide	387.5	75
	N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-[3-[2-(diethylamino)ethoxy]phenyl]-2-thienyl)urea trifluoroacetate	459.6	76

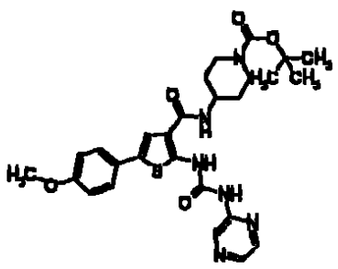
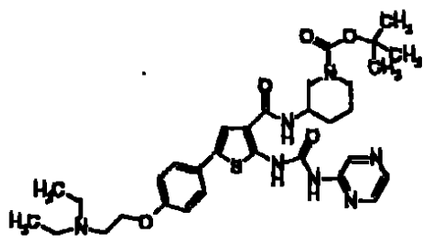
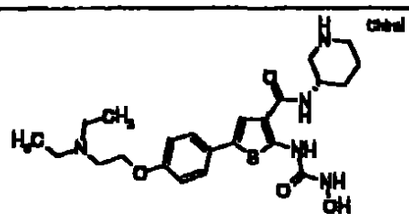
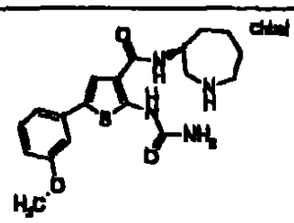
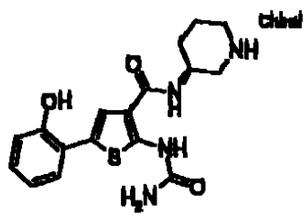
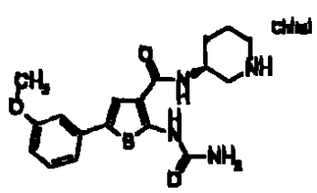
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide	388.5	77
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1,2,3,4-tetrahydroquinolin-3-yl)thiophene-3-carboxamide	422.5	78
	2-[(aminocarbonyl)amino]-N-(1,3-benzodioxol-5-ylmethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	425.5	79
	2-[(aminocarbonyl)amino]-N-(3-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	411.5	80
	2-[(aminocarbonyl)amino]-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide	455.5	81
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(5-methyl-2-furyl)methyl]thiophene-3-carboxamide	385.4	84
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-2-ylmethyl)thiophene-3-carboxamide	382.4	85

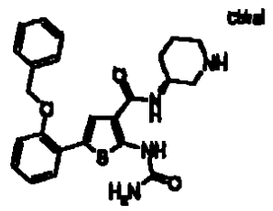
	2-[(aminocarbonyl)amino]-N-(4-fluorobenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	399.4	86
	tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	474.6	88
	2-[(aminocarbonyl)amino]-N-(2-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	411.5	89
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-phenoxyethyl)thiophene-3-carboxamide	411.5	90
	2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-2-ylethyl)thiophene-3-carboxamide	396.5	93
	tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate	474.6	94
	2-[(aminocarbonyl)amino]-N-(4-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide	411.5	95

	2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide trifluoroacetate	459.6	110
	2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide trifluoroacetate	459.6	111
	tert-butyl (3S)-3-[[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	559.7	112
	2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxamide hydrochloride	473.6	113
	tert-butyl (3R)-3-[[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	559.7	114
	N-[3-{[(3S)-3-aminoazepan-1-yl]carbonyl}-5-(4-methoxyphenyl)-2-thienyl]urea hydrochloride	388.5	115
	5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	523.7	120

	5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide hydrochloride	523.7	121
	5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	537.7	122
	N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide hydrochloride	466.6	123
	5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide hydrochloride	537.7	124
	N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	412.5	125
	5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	537.7	126

	5-(4-methoxyphenyl)-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	452.5	127
	tert-butyl 3-{[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate	637.8	128
	5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	537.7	129
	5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	438.5	130
	N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea	452.5	131
	N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea	438.5	132

	tert-butyl 4-{[(5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate	552.6	133
	tert-butyl 3-{[(5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate	637.8	134
	5-[4-(2-diethylamino-ethoxy)-phenyl]-2-(3-hydroxy-urea)-thiophene-3-carboxylic acid-(S)-piperidin-3-ylamide	475.2	136
	2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(3-methoxyphenyl)thiophene-3-carboxamide	388.5	137
	2-[(aminocarbonyl)amino]-5-(2-hydroxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	360.4	138
	2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide	374.5	139

	2-[(aminocarbonyl)amino]-5-[2-(benzyloxy)phenyl]-*N*-[(3*S*)-piperidin-3-yl]thiophene-3-carboxamide	450.6	140

Example 4

2-[(Aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide

(4-Methoxy-phenyl)-acetaldehyde. To a stirred solution of (4-Methoxy-phenyl)-acetic acid methyl ester (18.0 g, 100 mmol) in anhydrous toluene (200 mL) cooled to –78 °C under N_2 was added diisobutylaluminum hydride (DIBAL, 1.0 M in toluene, 150 mL, 150 mmol) over a period of 10-15 minutes. The mixture was stirred at –78 °C for an additional 2h. The reaction was quenched by the slow addition of MeOH, followed by the introduction of 10% Rochelle's Salt. The suspension was diluted with EtOAc and stirred at room temperature for 1h. The EtOAc layer was set aside and the aqueous layer was extracted with EtOAc(2x). The combined organic layers were combined and dried over Na_2SO_4 and filtered. The solution was concentrated under vacuum to yield 12.0 g (100%) of the title aldehyde as a yellow viscous semisolid, which was used in the next step without purification. LC/MS (APCI, ES, M+H=151).

2-Amino-5-(4-methoxy-phenyl)-thiophene-3-carboxylic acid methyl ester. To a solution of 4-methoxyphenylacetaldehyde (12.0g) in DMF (200mL) was added cyanomethyl acetate (8.9 mL, 100 mmol) and sulfur (3.2g, 100mmol), followed by diisopropylethylamine (Hunig's Base, 17.4 mL, 100 mmol). The resultant suspension immediately turned dark yellow to brown with an exotherm. The reaction mixture was stirred overnight at room temperature. The reaction was slowly added to water (~1L) while stirring. A tan precipitate formed and was filtered after an additional 30 minutes of stirring. The resultant solid was purified by column chromatography (SiO_2, 10-20% EtOAc/ hexanes) to yield 15.3 g (58%) of the title compound as a light yellow

solid. ^{1}H NMR (d_6-DMSO δ 7.41, br s, 2H; δ 7.37, d, 2H; δ 7.07, s, 1H; δ 6.90, d, 2H; δ 3.75, s, 3H; δ 3.72, s, 3H), LC/MS (APCI, ES, M+H=264).

Methyl 5-(4-methoxyphenyl)-2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate. To a stirred solution of 2-Amino-5-(4-methoxy-phenyl)-thiophene-3-carboxylic acid methyl ester (7.15 g, 27.2 mmol) in anhydrous THF (150 mL) was added trichloroacetyl isocyanate (6.4 mL, 54 mmol) slowly over a period of 5 min. After the addition was complete, a precipitate formed and the reaction stirred for an additional 1h. The desired product was obtained by filtration to give 6.9 g (56%) an off-white solid. The product was used in the next step without purification ^{1}H NMR (d_6-DMSO δ 12.3, br s, 1H; δ 12.2, s, 1H; δ 7.46, d, 2H; δ 7.32, s, 1H; δ 6.85, d, 2H; δ 3.75, s, 3H; δ 3.66, s, 3H), LC/MS (APCI, ES, M+H=451).

***tert*-Butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate.** To a solution of methyl 5-(4-methoxyphenyl)-2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate (1.0 g, 2.2 mmol) in dry THF (20 mL) was added a solution of [Me_2Al-3-Boc-(S)-3-aminopiperidine] in THF (which was preformed by the addition of Me_3Al (2.0 M in hexanes, 2.2 mL, 4.4 mmol) to a solution of (S)-3-Amino-piperidine-1-carboxylic acid tert-butyl ester (0.89 g, 4.4 mmol) in 10 mL THF at -78°C followed by warming to room temperature for an additional 15 min). The resulting orange-colored solution was stirred overnight at room temperature. The reaction mixture was cooled with ice and a 10% aqueous solution of Rochelle's salt was added slowly to quench the reaction. The resulting biphasic solution was warmed to room temperature and stirred for an additional 1h. The mixture was diluted with EtOAc and H_2O, the aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with H_2O, brine and dried (Na_2SO_4). Evaporation gave a pale orange solid. Purification by column chromatography (SiO_2, 50 % EtOAc/hexanes) gave 0.70 g (67%) of a light yellow solid. LC/MS (APCI, ES, M+H=475).

2-[(Aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3S)-piperidin-3-yl]thiophene-3-carboxamide; hydrochloride. To a stirred solution of *tert*-butyl (3S)-3-({[2-

[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate (0.70 g, 1.47 mmol) in anhydrous MeOH (5.0 mL) was added 4.0N HCl in 1, 4-dioxane (10 mL). A small amount of precipitate forms shortly and the reaction is stirred for an additional 4h at room temperature. The solvent was removed under vacuum. The residue was redissolved in methanol and concentrated under vacuum (2x) to yield 0.51 g (85%) of a light yellow solid. ^{1}H NMR (d_6-DMSO δ 10.9, s, 1H; δ 9.39, br s, 1H; δ 9.20, br s, 1H; δ 8.37, d, 1H; δ 7.88, s, 1H; δ 7.49, d, 2H; δ 6.96, d, 2H; δ 6.97, br s, 2H; δ 4.24, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.11, m, 1H; δ 2.93, m, 2H; δ 1.91, m, 2H; δ 1.68, m, 2H), LC/MS (APCI, ES, M+H=6875).

Example 26

2-[(Aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide hydrochloride

(S)-3-Amino-azepane-1-carboxylic acid tert-butyl ester. (S)-Azepan-3-ylamine (5g; 43.8 mmol) was dissolved in 100 mL of anhydrous CH_2Cl_2 and cooled to –78 °C while stirring with a magnetic stirring bar. In another flask N-(tert-butoxycarbonyloxy)succinimide [Boc-OSu] (9.7 g; 45 mmol) was dissolved in 50 mL of anhydrous CH_2Cl_2. To the stirred solution of the amine was added the solution of the succinimide over a period of 10-15 minutes so as to keep the reaction mixture at –78 °C while stirring. After the addition was complete, the reaction was allowed to warm to room temperature and then stirred for an additional 4h or until the reaction was complete by TLC (Ninhydrin; R_f 0.3; 0.1:1:10 NH_4OH, MeOH; CH_2Cl_2). The reaction mixture was washed with 50 mL of H_2O. The aqueous layer was brought to a pH >13 by the addition of 6N NaOH and extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was dried over Na_2CO_3, filtered, and concentrated in a vacuum to yield pure (S)-3-amino-azepane-1-carboxylic acid tert-butyl ester as a viscous oil (5.1 g, 54%). ^{1}H NMR (d_6-DMSO, d 3.4, m, 2H; d 2.89, m, 1H; d 2.71, m, 1H; d 2.54, m, 1H; d 1.54, m, 3H; d 1.34, m, 3H; d 1.27, s, 9H; d 1.12, m, 2H), LC/MS (APCI, ES, M+H=215).

***tert*-Butyl (3*S*)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azepane-1-carboxylate.** To a solution of methyl 5-(4-methoxyphenyl)-2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate (1.36 g, 3 mmol) in anhydrous THF (20 mL) was added a solution of [Me_2Al-3-Boc-(S)-3-aminohomopiperidine] in THF (preformed by the careful addition of Me_3Al (2.0 M in hexanes, 3.0 mL, 6.0 mmol) to a solution of (S)-3-amino-azepane-1-carboxylic acid tert-butyl ester in 10 mL of THF at –78 °C followed by warming to room temperature under nitrogen and stirring for an additional 15 min.). The resulting deep yellow/orange solution was stirred overnight at room temperature. The reaction mixture was cooled with ice and a 10% aqueous solution of Rochelle's salt was added slowly to quench the reaction. The resulting biphasic solution was warmed to room temperature and stirred for an additional 1h. The mixture was diluted with EtOAc and H_2O, the aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with H_2O, brine and dried (Na_2SO_4). Evaporation gave a pale orange solid. Purification by ISCO MPLC (SiO_2, 60-80% EtOAc/hexanes) gave 0.9 g (62%) of the title compound as a white solid. ^1H NMR (d_6-DMSO, δ 11.0, s, 1H; δ 7.95, d, 0.5H; δ 7.81, d, 0.5H; δ 7.65, s, 0.5H; δ 7.56, s, 0.5H; δ 7.46, d, 2H; δ 6.97, d, 2H; δ 6.96, br s, 2H; δ 4.19, m, 0.5H; δ 4.11, m, 0.5H; δ 3.77, m, 3H; δ 3.65, m, 1H; δ 3.48, m, 1H; δ 3.20, m, 2H; δ 1.75, m, 3H; δ 1.58, m, 2H; δ 1.42, s, 4.5H; δ 1.39, m, 1H; δ 1.36, s, 4.5H), LC/MS (APCI, ES, M+H=489).

2-[(Aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide; hydrochloride. To a stirred solution of *tert*-butyl (3*S*)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azepane-1-carboxylate (0.9g, 1.8 mmol) in 1, 4-dioxane (10 mL) was added 4.0N HCl in 1, 4-dioxane (10 mL, 40 mmol). A precipitate forms shortly and the reaction is stirred for an additional 4h at room temperature. Due to the hygroscopic nature of the salt form, the solvent was removed under vacuum. The residue was dissolved in methanol and concentrated under vacuum (2x) to yield and off-white solid. Recrystallization from using 2-propanol gave 0.45g (59%) of a white solid. ^1H NMR (d_6-DMSO, δ 10.9, s, 1H; δ 9.58, br s, 1H; δ 9.29, br s, 1H; δ 8.39, d, 1H; δ 7.82, s, 1H; δ 7.48, d, 2H; δ 6.96, d, 2H; δ 4.36, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.20, m, 2H; δ 3.07, m, 1H; δ 1.98, m, 1H; δ 1.84, m, 4H; δ 1.59, m, 1H), LC/MS (APCI, ES, M+H=389).

Example 110

2-[(Aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide trifluoroacetate To a stirred solution of *tert*-butyl (3*S*)-3-({[2-[(aminocarbonyl) amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate dissolved in a small amount of methanol was added 4.0 N HCl in dioxane. The solution was stirred for 1h at RT. The product was purified by Gilson (5%MeCN-H_2O→98%MeCN-H_2O) to yield 27 mg of the title compound as the trifluoroacetate salt. ^1H NMR (300 MHz, d_3-MeOD; δ 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.60(dd, 2H), 3.50(m, 1H), 3.30(m, 5H), 2.95(dd, 2H), 2.10(dd, 2H), 1.80(m, 2H), 1.35(t, 6H)), LCMS, (ES, M+H=460).

Example 112

tert-Butyl (3S)-3-{[(2-[(aminocarbonyl)amino]-5-[4-[2-(diethylamino)ethoxy]phenyl]-3-thienyl)carbonyl]amino}piperidine-1-carboxylate trifluoroacetate

Methyl [4-[2-(diethylamino)ethoxy]phenyl]acetate To a solution of methyl (4-hydroxyphenyl)acetate (16.6 g, 10 mmol) in DMF (100 mL) was added 2-bromo-*N*,*N*-diethylethanamine hydrobromide (2.6 g, 10 mmol) and), Cs_2CO_3 (6.6g, 20 mmol). After 1h an additional equivalent of the bromide was added and then stirred overnight at room temperature. The reaction mixtute was poured in to a large volume of cold water. The product was then isolated by filtration and purified by column chromatography (SiO_2, 10% MeOH/DCM) to give 15.6 g of the title compound as an off-white solid. LC/MS (APCI, ES, M+H=266).

[4-[2-(Diethylamino)ethoxy]phenyl]acetaldehyde To a stirred solution of methyl [4-[2-(diethylamino)ethoxy]phenyl]acetate (5.3 g, 20 mmol) in anhydrous toluene (100 mL) cooled to –78 °C under N_2 was added diisobutylaluminum hydride (DIBAL, 1.0M in toluene, 100 mL, 100 mmol) over a period of 10-15 minutes. The mixture was stirred at –78 °C for an additional 2h. The reaction was quenched by the slow addition of MeOH, followed by the introduction of 10% Rochelle's Salt. The suspension was diluted with EtOAc and stirred at room temperature for 1h. The EtOAc layer was set aside and the aqueous layer was extracted with EtOAc(2x). The

combined organic layers were combined and dried over Na_2SO_4 and filtered. The solution was concentrated under vacuum to yield 4.7 g (100%) of the title aldehyde as a yellow viscous semisolid, which was used in the next step without purification. LC/MS (APCI, ES, M+H=236).

Methyl 2-amino-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxylate To a solution of {4-[2-(diethylamino)ethoxy]phenyl}acetaldehyde (4.7 g, 20mmol) in DMF (30 mL) was added cyanomethyl acetate (1.5 mL, 20 mmol) and sulfur (0.6 g, 20mmol), followed by diisopropylethylamine (Hunig's Base, 2.5 mL, 20 mmol). The resultant suspension immediately turned dark yellow to brown with an exotherm. The reaction mixture was stirred overnight at room temperature. The reaction was slowly added to water (~200 mL) while stirring. A tan precipitate formed and was filtered after an additional 30 minutes of stirring. The resultant solid was purified by column chromatography (SiO_2, 5-10% MeOH/DCM/0.5% NH_4OH) to yield 2.4 g of the title compound as a light yellow solid. LC/MS (APCI, ES, M+H=349).

2-Amino-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxylic acid To a stirred solution of methyl 2-amino-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxylate (2.0 g, 5.7 mmol) in MeOH (50 mL) was added 6N NaOH (50 mL) and water (50 mL). The reaction was heated to reflux for 2h or until starting material was gone by TLC or LCMS. The solution was concentrated under vacuum to about half of the original volume. The pH of the resultant cloudy mixture was adjusted to 3-5 by the careful addition of 6N HCl (~150 mL) while stirring. The gummy red precipitate was filtered and dried. Purification was achieved by triturating in boiling hexanes. The product (1.6 g) was isolated in pure form by filtration after cooling to room temperature and drying in a vacuum oven overnight. LC/MS (APCI, ES, M+H=335).

***tert*-Butyl (3S)-3-{[(2-amino-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl) carbonyl] amino}piperidine-1-carboxylate** To a stirred solution of 2-amino-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxylic acid (100 mg, 0.3 mmol) in anhydrous DMF (2.0 mL) is added (S)-3-amino-azepane-1-carboxylic acid tert-butyl ester (60 mg, 0.3 mmol), EDCI (63 mg, 0.33 mmol), HOBt (61 mg, 0.45 mmol), and NMM (0.04 mL, 0.3 mmol). The reaction mixture was stirred overnight at room temperature. The solution was diluted with

water and EtOAc. The organic layer was separated and set aside. The remaining aqueous layer was extracted with EtOAc (2x) and then the combined organic extracts were pooled and washed with brine. The resultant EtOAc solution was dried over Na_2SO_4, filtered, and concentrated under vacuum to yield a brown solid. Purification was performed by Gilson (5%MeCN-H_2O→98%MeCN-H_2O) to give 90 mg of an off-white solid. LC/MS (APCI, ES, M+H=517).

***tert*-Butyl (3S)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate** To a stirred solution of *tert*-butyl (3S)-3-{[(2-amino-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl) carbonyl]amino}piperidine-1-carboxylate (90 mg, 0.17 mmol) in anhydrous THF (5.0 mL) was added trichloroacetyl isocyanate (0.09 mL, 0.7 mmol) slowly over a period of 5 min. After the addition was complete, a precipitate formed and the reaction stirred for an additional 1h. The reaction mixture was concentrated in a vacuum. The crude residue was dissolved in methanol and then charged with 2.0N NH_3 in methanol (0.35 mL). Purification by Gilson (5%MeCN-H_2O→98%MeCN-H_2O) gave the title (50 mg) as a tan solid. ^1H NMR (300 MHz, d_3-MeOD; δ 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 3.60-3.90(m, 3H), 3.60(dd, 2H), 3.30(m, 4H), 2.95(m, 2H), 1.90(dd, 2H), 1.55(m, 2H), 1.45(s, 9H), 1.35(t, 6H)), (APCI, ES, M+H=560).

Example 123....

N-[(3S)-Azepan-3-yl]-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide hydrochloride

2-Amino-5-(4-methoxy-phenyl)-thiophene-3-carboxylic acid. To a stirred solution of 2-amino-5-(4-methoxy-phenyl)-thiophene-3-carboxylic acid methyl ester (6.6 g, 26.6 mmol) in MeOH (200 mL) was added 6N NaOH (100 mL) and water (50 mL). The reaction was heated to reflux for 2h or until starting material was gone by TLC or LCMS. The solution was concentrated under vacuum to about half of the original volume. The pH of the resultant cloudy mixture was adjusted to 3-5 by the careful addition of 6N HCl (~150 mL) while stirring. The gummy red precipitate was filtered and dried. Purification was achieved by triturating in boiling hexanes. The product (6.0 g, 91%) was isolated in pure form by filtration after cooling to room

temperature and drying in a vacuum oven overnight. ^{1}H NMR (d_6-DMSO δ 7.37, d, 2H; δ 7.11, s, 1H; δ 7.10, br s, 2H; δ 6.94, d, 2H), LC/MS (APCI, ES, M+H=250).

Pyrazine-2-carboxylic acid hydrazide. To a stirred solution of pyrazine-2-carboxylic acid methyl ester (11.1 g, 80 mmol) in 140 mL of EtOH was added hydrazine hydrate (15.6 mL, 320 mmol). The resultant solution was heated to reflux for 2h. The solvent was removed under reduced pressure and dried under high vacuum to yield the title amide (11.1 g, 100%) as a white solid. The product was used in subsequent steps without purification. ^{1}H NMR (d_6-DMSO δ 10.1, br s, 1H; δ 9.12, d, 1H; δ 8.83, d, 1H; δ 8.70, dd, 1H; δ 4.64, br s, 2H), LC/MS (APCI, ES, M+H=139).

Pyrazine-2-carbonyl azide. Pyrazine-2-carboxylic acid hydrazide (11.1 g, 80 mmol) was dissolved in 140 mL of water and charged with 6N HCl (13.3 mL, 80 mmol) and cooled to 0 °C. To the stirred reaction mixture was added a solution of sodium nitrite (8.3 g, 120 mmol) in 80 mL of water was added slowly over a period of 15-30 minutes using an addition funnel. After the addition was complete the reaction was warmed to room temperature and stirred for an additional 5h. The solution was the neutralized by the careful addition of solid $NaHCO_3$ and then extracted with $CHCl_3$ (3x). The pooled organic fractions were dried over Na_2SO_4, filtered, concentrated and dried under high vacuum overnight to yield 2.5 g (21%) the title acyl azide. The product was used in subsequent steps without purification. ^{1}H NMR (d_6-DMSO δ 9.30, d, 1H; δ 9.03, d, 1H; δ 8.90, dd, 1H).

(S)-3-{[2-Amino-5-(4-methoxy-phenyl)-thiophene-3-carbonyl]-amino}-azepane-1carboxylic acid tert-butyl ester. To a stirred solution of 2-amino-5-(4-methoxy-phenyl)-thiophene-3-carboxylic acid (1.0 g, 4.0 mmol) in anhydrous DMF (20 mL) is added (S)-3-amino-azepane-1-carboxylic acid tert-butyl ester (1.03 g, 4.8 mmol), BOP (2.6 g, 6.0 mmol) and NMM (0.6 mL, 5 mmol). The reaction mixture was stirred overnight at room temperature. The solution was diluted with water and EtOAc. The organic layer was separated and set aside. The remaining aqueous layer was extracted with EtOAc (2x) and then the combined organic extracts were pooled and washed with brine. The resultant EtOAc solution was dried over Na_2SO_4, filtered,

and concentrated under vacuum to yield a brown solid. Purification was performed by ISCO MPLC (SiO_2, 30-50% EtOAc/hexanes) to give 0.9 g (50%) of an off-white solid. ^1H NMR (d_6-DMSO δ 7.51, d, 0.5H; δ 7.46, s, 0.5H; δ 7.37, s, 0.5H; δ 7.36, d, 0.5H; δ 7.34, br s, 2H; δ 7.33, d, 2H; δ 6.93, d, 2H; δ 4.11, br s, 1H; δ 3.76, s, 3H; δ 3.61, dq, 1H; δ 3.47, m, 1H; δ 3.11, m, 2H; δ 1.73, m, 3H; δ 1.56, m, 2H; δ 1.42, s, 4.5H; δ 1.38, s+m, 5.5H;), LC/MS (APCI, ES, M+H=446).

***tert*-Butyl (3*S*)-3-{[(5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}azepane-1-carboxylate.** A solution of (S)-3-{[2-amino-5-(4-methoxyphenyl)-thiophene-3-carbonyl]-amino}-azepane-1carboxylic acid tert-butyl ester (0.76 g, 1.7 mmol) and pyrazine-2-carbonyl azide (0.5 g, 3.4 mmol) in 20 mL of anhydrous DME was refluxed for 2h. The solvent was removed under reduced pressure and the crude product was purified using ISCO MPLC (40-60% EtOAc/hexanes) to give the title 0.51 g (53%) compound as a light yellow solid. ^1H NMR (d_6-DMSO δ 12.5, br s, 0.5H; δ 12.4, br s, 0.5H; δ 10.90, s, 0.5H; δ 10.88, s, 0.5H; δ 8.93, s, 0.5H; δ 8.89, s, 0.5H; δ 8.33, d, 1H; δ 8.29, t, 1H; δ 8.05, d, 0.5H; δ 7.91, d, 0.5H; δ 7.74, s, 0.5H; δ 7.65, s, 0.5H; δ 7.52, dd, 2H; δ 7.00, d, 2H; δ 4.26, m, 0.5H; δ 4.17, m, 0.5H; δ 3.79, s, 3H; δ 3.69, m, 1H; δ 3.48, m, 1H; δ 3.21, m, 2H; δ 1.77, m, 3H; δ 1.61, m, 2H; δ 1.44, s, 4.5H; δ 1.38, s+m, 5.5H), LC/MS (APCI, ES, M+H=567).

***N*-[(3*S*)-Azepan-3-yl]-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide; hydrochloride.** To a stirred solution of *tert*-butyl (3*S*)-3-{[(5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}azepane-1-carboxylate (0.51 g, 0.9 mmol) in 10 mL of MeOH is added 10 mL (40 mmol) of 4.0 N HCl in dioxane. The solution was stirred at room temperature for 4h and then concentrated under vacuum. The residue was partially recrystallized by triturating in refluxing 2-propanol to yield the title compound are a light orange solid (0.30 g, 67%). ^1H NMR (d_6-DMSO δ 12.6, br s, 1H; δ 10.9, s, 1H; δ 9.55, br s, 1H; δ 9.24, br s, 1H; δ 8.88, s, 1H; δ 8.49, d, 1H; δ 8.35, dd, 1H; δ 8.29, d, 1H; δ 7.92, s, 1H; δ 7.54, d, 2H; δ 6.99, d, 2H; δ 4.42, m, 1H; δ 3.33, m, 1H; δ 3.23, m, 2H; δ 3.10, m, 1H; δ 2.02, m, 1H; δ 1.85, m, 4H; δ 1.62, m, 1H;), LC/MS (APCI, ES, M+H=467).

Example 136

2-[(Aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide trifluoroacetate

tert-Butyl (3*S*)-3-{[(5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(hydroxyamino) carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate To a solution of *tert*-butyl (3*S*)-3-{[(2-amino-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl) carbonyl] amino}piperidine-1-carboxylate (115 mg, 0.22 mmol) in THF (640 µL) was added 1,1'-carbonyl diimidazole (178 mg, 1.1 mmol). The resulting cloudy solution was stirred at rt for 1 h whereupon hydroxylamine hydrochloride (76.4 mg, 1.1 mmol) and Et_3N (100 µL) were added and the resulting dark solution was stirred for 48 h at rt. The mixture was partitioned between EtOAc and H_2O and the organic layer was washed with H_2O, brine and dried ($MgSO_4$). Evaporation afforded a yellow residue. Purification by Gilson (5%MeCN-H_2O→98%MeCN-H_2O) gave the title hydroxy urea.

5-{4-[2-(Diethylamino)ethoxy]phenyl}-2-{[(hydroxyamino)carbonyl]amino}-*N*-[(3*S*)-piperidin-3-yl]thiophene-3-carboxamide A stirred solution of *tert*-butyl (3*S*)-3-{[(5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(hydroxyamino)carbonyl]amino}-3-thienyl) carbonyl]amino}piperidine-1-carboxylate in dioxane was treated with 4.0N HCl solution in dioxane (3 mL) and the resulting cloudy mixture was stirred at rt for 1 h. Evaporation of the solvent gave 5-[4-(2-diethylamino-ethoxy)-phenyl]-2-(3-hydroxy-urea)-thiophene-3-carboxylic acid-(S)-piperidin-3-ylamide as the hydrochloride salt (8 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.17 - 1.40 (m, 6 H) 1.54 - 1.81 (m, 2 H) 1.84 - 2.07 (m, 2 H) 2.76 - 2.99 (m, 2 H) 3.05 - 3.25 (m, 4 H) 3.41 - 3.61 (m, 4 H) 3.73 - 3.88 (m, 1 H) 4.29 - 4.42 (m, 1 H) 4.40 - 4.64 (m, 1 H) 5.86 (s, 1 H) 7.07 (d, *J*=8.48 Hz, 2 H) 7.55 (d, *J*=8.48 Hz, 2 H) 7.82 (s, 1 H) 9.44 (s, 1 H) 9.65 (s, 1 H); LC/MS (ES, M+H=476).

Example 137

2-[(Aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(3-methoxyphenyl)thiophene-3-carboxamide

tert-Butyl (3S)-3-[({2-[(aminocarbonyl)amino]-5-bromo-3-thienyl} carbonyl)amino]azepane-1-carboxylate

To a solution of methyl 2-[(aminocarbonyl)amino]-5-bromothiophene-3-carboxylate (1 equiv) in dry THF (0.3 M) was added a solution of [Me_2Al-Boc-3-(S)-aminohomopiperidine] (2 equiv) in THF (1.0 M) (which was preformed by the addition of Me_3Al (2.0 M in hexanes) to a solution of Boc-3-(S)-homopiperidine in THF at –78 °C and the resulting yellow solution was warmed to room temperature and stirred for an additional 15 min) and the resulting deep yellow solution was stirred overnight at room temperature. The reaction mixture was cooled with ice and a 10% aqueous solution of Rochelle's salt was added slowly to quench the reaction. The resulting biphasic solution was warmed to room temperature and stirred for an additional 1h. The mixture was diluted with EtOAc and H_2O, the aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with H_2O, brine and dried ($MgSO_4$). Evaporation gave a pale orange solid. Purification by column chromatography (40-60% EtOAc/Hexanes) gave a white solid. LC/MS (ES, M+H=462).

tert-Butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)azepane-1-carboxylate A flask was loaded with *tert*-butyl (3S)-3-[({2-[(aminocarbonyl)amino]-5-bromo-3-thienyl} carbonyl)amino]azepane-1-carboxylate (1.0 mmol), 3-methoxyphenylbotonic acid (1.5 mmol), Cs_2CO_3 (3.0 mmol) and $Pd(PPh_3)_4$ (0.05-0.1 mmol) and was purged with nitrogen for 10 mins. Dioxane (4mL) and H_2O (1mL) were added under nitrogen atmosphere and the resulting mixture was heated to 90°C for 2-4h. The mixture was allowed to cool to RT and the mixture was filtered (0.45 uM or diatomaceous earth). The water layer was separated and remaining solvent was concentrated to dryness. The residue was purified by column chromatography (SiO_2) on an MPLC ISCO separation system (30-60% EtOAc/hexanes) to give an off-white solid. LCMS, (ES, M+H=489).

2-[(Aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(3-methoxyphenyl)thiophene-3-carboxamide hydrochloride To a stirred solution of *tert*-butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)azepane-1-carboxylate

dissolved in a small amount of methanol was added 4.0 N HCl in dioxane. The solution was stirred for 1h at RT. The product as the hydrochloride salt was obtained as an off-white solid after removal of the solvent and drying. ^{1}H NMR (d_6-DMSO δ 10.90 (s, 1H), 9.21 (s, 1H), 9.01 (s, 1H), 8.29 (d, 1H), 7.93 (s, 1H), 7.29 (t, 1H), 7.11 (d, 2H), 7.03 (s, 1H), 6.83 (d, 1H), 4.33 (s, 1H), 3.81 (s, 3H), 3.20 (m, 4H), 2.00 (m, 1H), 1.84 (m, 4H), 1.56 (m, 1H)), LCMS, (ES, M+H=389).

Example 139

2-[(Aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide

Methyl 2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate. To a stirred solution of 2-amino-thiophene-3-carboxylic acid methyl ester (1 eq) in anhydrous THF (mL) was added trichloroacetyl isocyanate (1 eq) slowly over a period of 5 min. After the addition was complete, a precipitate formed and the reaction stirred for an additional 1h. The desired product was obtained by filtration to give methyl 2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate (99%) as an off-white solid. The product was used in the next step without any further purification. LC/MS (ES, M+H=345).

Methyl 5-bromo-2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate. To a stirred solution of methyl 2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate (1 eq) in glacial acetic acid (20 mL) was added a solution of bromine (1.3 eq) in glacial acetic acid (5 mL) slowly over a period of 5 min. After the addition was complete, the resulting dark solution was stirred for 30 mins at RT. The solvent was evaporated under vaccum and the residue was triturated with H_2O. The title compound was obtained by filtration (99%) as an off-white solid. The product was used in the next step without any further purification after drying for 2 days under P_2O_5. LC/MS (ES, M+H=425).

Methyl 2-[(aminocarbonyl)amino]-5-bromothiophene-3-carboxylate. A stirred solution of methyl 5-bromo-2-({[(trichloroacetyl)amino]carbonyl}amino)thiophene-3-carboxylate (1 eq) in

anhydrous methanol was purged with dry ammonia for 20 mins. After stirring for extra 10 mins at RT, precipitation was observed and the product was isolated by filtration (100% yield). LC/MS (ES, M+H=280).

***tert*-Butyl(3S)-3-[({2-[(aminocarbonyl)amino]-5-bromo-3-thienyl}carbonyl)amino] piperidine-1-carboxylate**

To a solution of methyl 2-[(aminocarbonyl)amino]-5-bromothiophene-3-carboxylate (1 equiv) in dry THF (0.3 M) was added a solution of [Me_2Al-Boc-3-(S)-aminopiperidine] (2 equiv) in THF (1.0M) (which was preformed by the addition of Me_3Al (2.0M in hexanes) to a solution of Boc-3-(S)-piperidine in THF at -78°C and the resulting yellow solution was warmed to room temperature and stirred for an additional 15 min) and the resulting deep yellow solution was stirred overnight at room temperature. The reaction mixture was cooled with ice and a 10% aqueous solution of Rochelle's salt was added slowly to quench the reaction. The resulting biphasic solution was warmed to room temperature and stirred for an additional 1h. The mixture was diluted with EtOAc and H_2O, the aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with H_2O, brine and dried ($MgSO_4$). Evaporation gave a pale orange solid. Purification by column chromatography (40-60% EtOAc/Hexanes) gave a white solid. ^1H NMR (d_6-DMSO, δ 10.9, s, 1H; δ 9.48, br s, 1H; δ 9.31, br s, 1H; δ 8.48, d, 1H; δ 8.10, s, 1H; δ 7.57, d, 2H; δ 7.38, t, 2H; δ 7.23, t, 1H; δ 7.01, br s, 2H; δ 4.26, m, 1H; δ 3.29, m, 1H; δ 3.11, m, 1H; δ 2.94, m, 2H; δ 1.91, m, 2H; δ 1.69, m, 2H), LC/MS (APCI, ES, M+H=345).

***tert*-Butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate** A flask was loaded with *tert*-butyl(3S)-3-[({2-[(aminocarbonyl)amino]-5-bromo-3-thienyl}carbonyl)amino] piperidine-1-carboxylate (1.0 mmol), 3-methoxyphenylboronic acid (1.5 mmol), Cs_2CO_3 (3.0 mmol) and $Pd(PPh_3)_4$ (0.05-0.1 mmol) and was purged with nitrogen for 10 mins. Dioxane (4 mL) and H_2O (1 mL) were added under nitrogen atmosphere and the resulting mixture was heated to 90 °C for 2-4h. The mixture was allowed to cool to RT and the mixture was filtered (0.45 uM or diatomaceous earth). The water layer was separated and remaining solvent was concentrated to dryness. The residue was

purified by column chromatography (SiO_2) on an MPLC ISCO separation system (30-60% EtOAc/hexanes) to give an off-white solid. LCMS, (ES, M+H=475).

2-[(Aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide hydrochloride To a stirred solution of *tert*-butyl (3*S*)-3-({[2-[(aminocarbonyl) amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate dissolved in a small amount of methanol was added 4.0 N HCl in dioxane. The solution was stirred for 1h at RT. The product as the hydrochloride salt was obtained as an off-white solid after removal of the solvent and drying. ^{1}H NMR (d_6-DMSO δ 10.94 (s, 1H), 9.41 (s, 1H), 9.19 (s, 1H), 8.47 (d, 1H), 8.11 (s, 1H), 7.30 (t, 1H), 7.15 (d, 1H), 7.05 (bt, 2H), 6.84 (d, 1H), 4.25 (s, 1H), 3.82 (s, 3H), 3.29 (d, 1H), 3.12 (d, 1H), 2.97 (m, 2H), 1.92 (d, 2H), 1.69 (m, 2H)), LCMS, (ES, M+H=375).

Other Examples

Examples 1-3, 5-25, and 27-109 were prepared in a similar fashion to that described for examples 4 and 26.

Examples 111 and 113-115 were prepared in a similar fashion to that described for examples 110 and 112.

Examples 116-119 were prepared according to the general Scheme V.

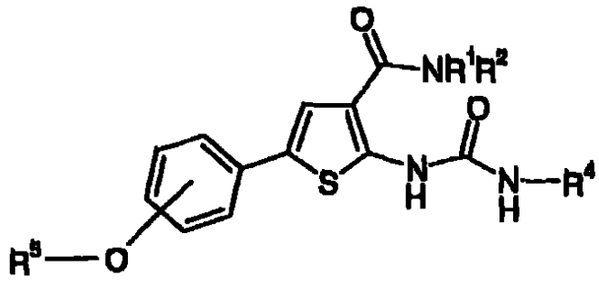
Examples 121-122 and 124-135 were prepared in a similar fashion to that described for examples 123 and 136.

Examples 138 and 140 were prepared in a similar fashion to that described for examples 137 and 139.

Claims

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or *in vivo*-hydrolysable precursors thereof:



(I)

wherein:

R^1 and R^2 are at each occurrence independently selected from H, optionally substituted C_{1-6}alkyl, or optionally substituted heterocyclyl; with the proviso that R^1 and R^2 are not both H; or R^1 and R^2 and the N to which they are attached in combination form an optionally substituted heterocyclyl;

R^4 is selected from H, OH, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted C_{1-6}alkyl;

R^5 is selected from H, optionally substituted carbocyclyl, or optionally substituted C_{1-6}alkyl.

2. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^2, R^4, and R^5 have any of the meanings defined in claim 1 and

R^1 is an optionally substituted heterocyclyl.

3. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^2, R^4, and R^5 have any of the meanings defined in claim 1 and R^1 is an optionally substituted heterocyclyl wherein 1,2, or 3 substitutents is/are independently selected from halogen, nitro, amino, cyano, trifluoromethyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, hydroxy, alkylhydroxy, carbonyl, $-CH(OH)CH_3$, $-CH_2NH$-alkyl-OH,

alkyl-(OH)CH_3, -CH_2-phenyl-(OCH_3)$_2$, -Oalkyl, -OCH_3, -Ophenyl, -OCOalkyl, -NHCHO, -Nalkyl, -N-(alkyl)-CHO, -NH-CO-amino, -N-(alkyl)-CO-amino, -NH-COalkyl, -N-(alkyl)-COalkyl, -carboxy, -amidino, -CO-amino, -CO-alkyl, -CO_2alkyl, mercapto, -Salkyl, -SCH_2furanyl, -SO(alkyl), -SO_2(alkyl), -SO_2-amino, -alkylsulfonylamino, phenyl, anisole, dimethoxyphenyl, trimethoxyphenyl, halophenyl, cycloalkyl, heterocyclyl, -alkyl-NH-cycloalkyl, -alkyl-NH- heterocyclyl, -alkyl-NH-alkyl-OH, -C(=O)OC(CH_3)$_3$, -N(CH_3)$_2$, -N(CH_2CH_3)$_2$, -alkyl-NH-alkyl- heterocyclyl, -alkyl-aryl, -methyl-phenyl, alkyl-polycyclyl, alkyl-amino, alkyl-hydroxy, -CH_2NH-alkyl-heterocyclyl, -CH_2NHCH2CH(CH_3)$_2$, vicinal -O(alkyl)O-, vicinal -OC(haloalkyl)O-, vicinal -CH_2O(alkyl)O-, vicinal -S(alkyl)S- and –O(alkyl)S-.

4. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^2, R^4, and R^5 have any of the meanings defined in claim 1 and R^1 is an optionally substituted heterocyclyl wherein 1,2, or 3 substitutents is/are independently selected from: -OH, C(=O)OC(CH_3)$_3$, NH_2, C_{1-6}alkyl, methoxybenzene, or dimethoxy benezene.

5. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^2, R^4, and R^5 have any of the meanings defined in claim 1 and

R^1 is a heterocyclyl wherein heterocyclyl is selected from piperdinyl, pyridinyl, pyrrolidinyl, pyrazinyl, azepanyl, azetidinyl, azabicyclozinyl, furanyl, thienyl.

6. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^1, R^4, and R^5 have any of the meanings defined in claim 1 and

R^2 is H.

7. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^1, R^2, and R^5 have any of the meanings defined in claim 1 and

R^4 is H.

8. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^1, R^2, and R^4 have any of the meanings defined in claim 1 and

R^5 is H or an optionally substituted C_{1-6}alkyl.

9. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^1, R^2, and R^4 have any of the meanings defined in claim 1 and

R^5 is H or an optionally substituted C_{1-6}alkyl wherein 1,2 or 3 substitutents is/are independently selected from: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH3, OH, -C_{1-6}alkyl, morpholino, piperidinyl, pyrrolodinyl.

10. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^1, R^2, and R^4 have any of the meanings defined in claim 1 and

R^5 is H or an optionally substituted C_{1-3}alkyl.

11. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof as recited in claim 1 wherein R^1, R^2, and R^4 have any of the meanings defined in claim 1 and

R^5 is H or an optionally substituted C_{1-3}alkyl wherein 1,2 or 3 substitutents is/are independently selected from: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH3, OH, -C_{1-6}alkyl, morpholino, piperidinyl, pyrrolodinyl.

12. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof, as recited in claim 1 wherein:

R^1 is an optionally substituted heterocyclyl;

R^2 is H;

R^4 is H;

R^5 is H or an optionally substituted C_{1-6}alkyl.

13. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof, as recited in claim 1 wherein:

R^1 is an optionally substituted heterocyclyl wherein the substitutent is selected from one or more of the following: $-NH_2$, C_{1-6}alkyl, $-C(=O)OC(CH_3)_3$,

R^2 is H;

R^4 is H;

R^5 is H or an optionally substituted C_{1-6}alkyl wherein the substitutent is selected from one or more of the following: $-C_{1-6}$alkyl, $-N(C_{1-3}alkyl)_2$.

14. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof, as recited in claim 1 wherein:

R^1 is an optionally substituted heterocyclyl wherein the substitutent is selected from one or more of the following: $-NH_2$, C_{1-6}alkyl, $-C(=O)OC(CH_3)_3$,

R^2 is H;

R^4 is H;

R^5 is H or an optionally substituted C_{1-3}alkyl wherein 1,2 or 3 substitutents is/are independently selected from: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH3, OH, $-C_{1-6}$alkyl, morpholino, piperidinyl, pyrrolodinyl.

15. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof, as recited in claim 1 wherein:

R^1 is a heterocyclyl;

R^2 is H;

R^4 is H;

R^5 is H or a C_{1-6}alkyl.

16. A compound of formula (I) or a pharmaceutically salt or an *in vivo*-hydrolysable precursor thereof, as recited in claim 1 wherein:

R^1 is a 6-membered heterocyclyl containing at least one N in the ring;

R^2 is H;

R^4 is H;

R^5 is a C_{1-3}alkyl.

17. A compound of formula (I) selected from:

tert-butyl 3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide;

tert-butyl 3-{[(2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[(3R)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-{4-[2-(diethylamino)ethoxy]phenyl}-2-thienyl)urea;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(2-aminoethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-pyridin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1-methylpiperidin-4-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylazepan-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-[3-(hydroxymethyl)phenyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-pyridin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}-N-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-pyrrolidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[2-(dimethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[2-(diethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(piperidin-4-ylmethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(1-ethylpiperidin-3-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-[(3S)-1-ethylazepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(3-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

tert-butyl (3S)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)pyrrolidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(1-benzylpiperidin-4-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-[4-(2-piperidin-1-ylethoxy)phenyl]-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-azetidin-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(2S)-pyrrolidin-2-ylmethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-pyridin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperidin-1-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-1-azabicyclo[2.2.2]oct-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(2-hydroxyethyl)-5-(4-hydroxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-(trans-4-hydroxycyclohexyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-piperazin-1-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-4-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-3-ylethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(2-methoxyphenyl)-N-piperidin-4-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(tetrahydrofuran-2-ylmethyl)thiophene-3-carboxamide;

tert-butyl (3R)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-3-ylmethyl)thiophene-3-carboxamide;

tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azetidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-4-ylmethyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(3-methoxypropyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]urea;

2-[(aminocarbonyl)amino]-N-(2-methoxyethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-(2-thienylmethyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-N-{2-[(2-furylmethyl)thio]ethyl}-5-(4-methoxyphenyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-hydroxyphenyl)-N-[2-(2-thienyl)ethyl]thiophene-3-carboxamide;
N-(3-[(4-aminopiperidin-1-yl)carbonyl]-5-{3-[2-(diethylamino)ethoxy]phenyl}-2-thienyl)urea;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-ylmethyl]thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1,2,3,4-tetrahydroquinolin-3-yl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-N-(1,3-benzodioxol-5-ylmethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-N-(3-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(5-methyl-2-furyl)methyl]thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(pyridin-2-ylmethyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-N-(4-fluorobenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;
tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;
2-[(aminocarbonyl)amino]-N-(2-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-phenoxyethyl)thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(2-pyridin-2-ylethyl)thiophene-3-carboxamide;
tert-butyl 4-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;
2-[(aminocarbonyl)amino]-N-(4-methoxybenzyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3S)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-N-[(3R)-piperidin-3-yl]thiophene-3-carboxamide;

tert-butyl (3S)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxamide;

tert-butyl (3R)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

N-[3-{[(3S)-3-aminoazepan-1-yl]carbonyl}-5-(4-methoxyphenyl)-2-thienyl]urea;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

N-[(3S)-azepan-3-yl]-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

tert-butyl 3-{[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea;

N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)-2-thienyl]-N'-pyrazin-2-ylurea;

tert-butyl 4-{[(5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

tert-butyl 3-{[(5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

5-[4-(2-diethylamino-ethoxy)-phenyl]-2-(3-hydroxy-urea)-thiophene-3-carboxylic acid-(S)-piperidin-3-ylamide;

2-[(aminocarbonyl)amino]-N-[(3S)-azepan-3-yl]-5-(3-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(2-hydroxyphenyl)-*N*-[(3*S*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(3-methoxyphenyl)-N-[(*3S*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-[2-(benzyloxy)phenyl]-*N*-[(*3S*)-piperidin-3-yl]thiophene-3-carboxamide.

18. A compound of formula (I) or a pharmaceutically acceptable salt thereof as recited in any one of claims 1 to 17 for use as a medicament.

19. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as recited in any one of claims 1 to 17, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with cancer.

20. A method for the treatment of cancer comprising administering to a human a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17.

21. A method for the treatment of breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma by administring a compound of formula I or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17.

22. A method of treating cancer by administering to a human a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17 and an anti-tumor agent.

23. A method of treating cancer by administering to a human a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17 and a DNA damaging agent.

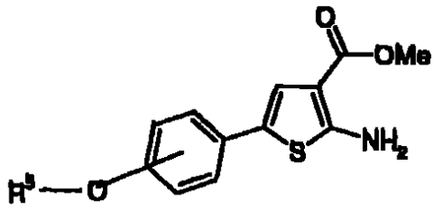
24. A method for the treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17.

25. A method for the prophylaxis treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17.

26. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 17 together with at least one pharmaceutically acceptable carrier, diluent or excipent.

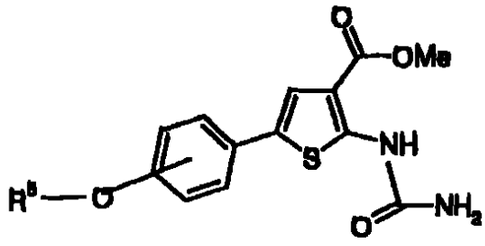
27. A process for the preparation of a compound of formula (I) or a phrmaceutically acceptable salt or *in vivo*-hydrolysable precursors thereof as defined in any one of claims 1 to 17, which comprises:

(a) the reaction of a 2-aminothiophene shown below as Formula II



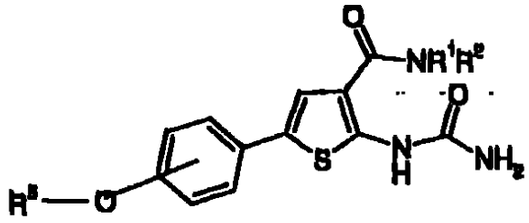
II

wherein the hydrogen at the 2-amino position is displaced to form an amide, shown as formula III below



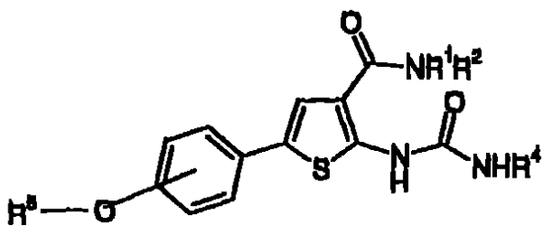
III

wherein the methyl ester is converted to an amide utilizing the desired amine in conjuntion with an aluminate organometallic complex, to give the product shown as formula IV below:



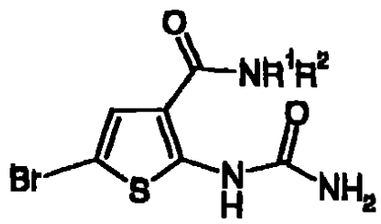
IV

Wherein the amide is converted to various substituted secondary ureas by the reaction with various isocyanantes to yield the product shown as fromula V below:



V

28. The use of a compound of formula (VI) below or a pharmaceutically acceptabl salt or an in vivo hydrolysable precursor in the manufacture of a compound of formula (I) as set forth in any one of claims 1-17.



VI

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003473

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D333/38 C07D409/12 A61K31/38 A61P35/00
//(C07D409/12,333:00,333:00),(C07D409/12,333:00,307:00),(C07D409/12 333:00,241:00)

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 C07D 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, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/029241 A (PARRISH CYNTHIA A ; SMITHKLINE BEECHAM CORP (US); HOLT DENNIS A (US);) 10 April 2003 (2003-04-10) scheme II; claim 5; example 28	1,6,8, 10,18-28
A	WO 03/028731 A (PARRISH CYNTHIA A ; SMITHKLINE BEECHAM CORP (US); HOLT DENNIS A (US);) 10 April 2003 (2003-04-10) claim 6	1-27
A	WO 02/070494 A (ICOS CORP) 12 September 2002 (2002-09-12) examples 1-6	1-27

☐ 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
4 November 2004	19/11/2004

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	Bakboord, J

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003473

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20-25
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003473

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03029241 A	10-04-2003	WO 03029241 A1	10-04-2003
WO 03028731 A	10-04-2003	WO 03028731 A1	10-04-2003
WO 02070494 A	12-09-2002	CA 2439709 A1	12-09-2002
		EP 1379510 A1	14-01-2004
		JP 2004523568 T	05-08-2004
		NO 20033858 A	10-10-2003
		WO 02070494 A1	12-09-2002
		US 2003069284 A1	10-04-2003

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
24 de Febrero de 2005 (24.02.2005)

(10) Número de Publicación Internacional
PCT WO 2005/016909 A1

(51) Clasificación Internacional de Patentes[7]: C07D 333/38 409/12, A61K 31/38, A61P 35/00 // (C07D 409/12, 333:00, 333:00) (C07D 409/12, 333:00, 307:00) (C07D 409/12, 333:00, 241:00)

(21) No. Solicitud Internacional: PCT/GB2004/003473

(22) Fecha de Presentación Internacional:
12 de agosto de 2004 (12.08.2004)

(25) Idioma de Presentación: inglés

(26) Idioma de Publicación: inglés

(30) Datos relativos a la Prioridad:
60/495,580 15 de agosto de 2003 (15.08.2003) US
60/575,416 28 de mayo de 2004 (28.05.2004) US

(71) Solicitante *(para todos los países destinatarios con excepción de MG, US)*: ASTRAZENECA AB [SE/SE]; SE-151 85 Södertälje (SE).

(71) Solicitante *(para US únicamente)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: ASHWELL, Susan [GB/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). GERO, Thomas [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). IOANNIDIS, Stephanos [GR/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). JANETKA, James [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). LYNE, Paul [IE/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). OZA, Vibha [IN/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). SPRINGER, Stephanie [US/US]; 37 Village Green Drive, North Andover, MA 01845 (US). SU, Mei [CN/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). YU, Dingwei [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US).

(74) Agente: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, SE-151 85 Södertälje (SE)

(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, 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) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:
— *con informe internacional de búsqueda*

Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

WO 2005/016909 A1

(54) Título: TIOFENOS SUSTITUIDOS Y SUS USOS

(57) Extracto: Esta invención se refiere a compuestos novedosos que tienen la fórmula estructural (I) y a sus sales farmacéuticas, composiciones y métodos de uso. Estos novedosos compuestos proporcionan un tratamiento o profilaxis del cáncer.

TIOFENOS SUSTITUIDOS Y SUS USOS

Campo de la Invención

La presente invención se refiere a novedosos tiofenos sustituidos, a sus composiciones farmacéuticas y a métodos de empleo. Adicionalmente, la presente invención se relaciona con métodos terapéuticos para el tratamiento y prevención de neoplasias malignas.

Antecedentes de la Invención

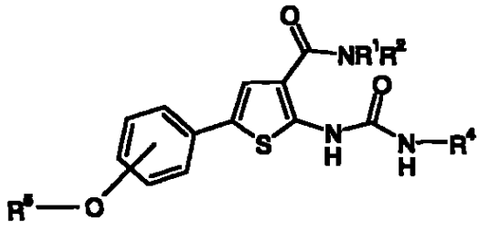
La quimioterapia y la exposición a radiación son actualmente las principales opciones para el tratamiento del cáncer, pero la utilidad de estos dos enfoques se ve severamente limitada por los efectos adversos sobre el tejido normal y el desarrollo frecuente de resistencia de las células tumorales. Por lo tanto, es deseable mejorar la eficacia de tales tratamientos en una forma que no aumente la toxicidad asociada con ellos. Un modo de lograr esto es mediante el uso de agentes sensibilizantes específicos, tales como los descritos aquí.

Una célula individual se replica haciendo una copia exacta de sus cromosomas y, luego, segregándolos en células separadas. Este ciclo de replicación de ADN, separación de cromosomas y división es regulado por mecanismos dentro de las células que mantienen el orden de los pasos y garantizan que cada paso se lleve a cabo con precisión. Involucrados en estos procesos se encuentran los puntos de control del ciclo celular (Hartwell *y colaboradores*, Science, Nov 3, 1989, 246 (4930): 629-34), donde las células se pueden detener para garantizar que los mecanismos de reparación del ADN tengan tiempo de operar, antes de proseguir las etapas del ciclo a la mitosis. Existen dos de tales puntos de control en el ciclo celular – el punto de control G1/S que se regula por p53 y el punto de control G2/M que se monitorea por el punto de control Ser/Thr cinasa 1 (CHK1).

La detención del ciclo celular inducida por estos puntos de control es un mecanismo mediante el cual las células pueden superar el daño resultante de la radio- o la quimioterapia; su supresión por agentes novedosos debería aumentar la sensibilidad de las células neoplásicas a las terapias que tienen como objetivo la destrucción del ADN (***"DNA damaging therapies"***). Adicionalmente, la supresión específica en el tumor del punto de control G1/S por mutaciones de p53 puede aprovecharse en la mayoría de los tumores para proporcionar agentes selectivos del tumor. Un enfoque al diseño de quimiosensibilizadores que suprimen el punto de control G2/M es desarrollar inhibidores de la cinasa reguladora clave de G2/M, la CHK1, y este enfoque ha demostrado ser eficaz en un número de análisis de estudios conceptuales. (Koniaras *y colaboradores*, *Oncogene*, 2001, 20: 7453; Luo *y colaboradores*, *Neoplasia*, 2001, 3: 411; Busby *y colaboradores*, *Cancer Res.*, 2000, 60: 2108; Jackson *y colaboradores*, *Cancer* Res., 2000, 60: 566).

Sumario de la Invención

Se proveen aquí compuestos novedosos de la fórmula estructural (I) o su sal farmacéuticamente aceptable:



(I)

en donde:

R^1 y R^2 en cada ocurrencia se seleccionan independientemente de H, opcionalmente sustituido C_{1-6}alquilo, o heterociclilo opcionalmente sustituido; con la condición que R^1 y R^2 no son ambos H; ó R^1 y R^2 y el N, al cual se unen, forman en combinación un heterociclilo opcionalmente sustituido;

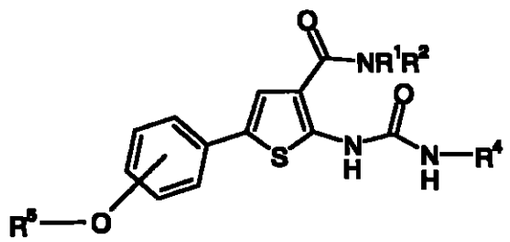
R^4 se selecciona de H, OH, carbociclilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido;

R^5 se selecciona de H, carbociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido.

La invención abarca igualmente estereoisómeros, enantiómeros, precursores hidrolizables *in vivo* y sales farmacéuticamente aceptables de compuestos de fórmula I, composiciones y formulaciones farmacéuticas que los contienen, métodos de usarlos para tratar enfermedades y afecciones, solos o en combinación con otros compuestos o sustancias terapéuticamente activos, procesos e intermedios usados para prepararlos, sus usos como medicamentos, sus usos en la manufactura de medicamentos y sus usos para fines de diagnóstico y análisis.

Descripción Detallada de la invención

Se proveen aquí compuestos novedosos de la fórmula estructural (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*:



(I)

en donde:

R^1 y R^2 en cada ocurrencia se seleccionan independientemente de H, C_{1-6}alquilo opcionalmente sustituido, o heterociclilo opcionalmente sustituido; con la condición que R^1 y R^2 no sean ambos H; ó R^1 y R^2 y el N, al cual se unen, formen en combinación un heterociclilo opcionalmente sustituido;

R^4 se selecciona de H, OH, carbociclilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido;

R^5 se selecciona de H, carbociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, en donde R^1 es un heterociclilo opcionalmente sustituido.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, en donde R^1 es un heterociclilo opcionalmente sustituido en donde 1, 2, ó 3 sustituyentes se selecciona/seleccionan de halógeno, nitro, amino, ciano, trifluorometilo, alquilo, alquenilo, alquinilo, haloalquilo, alcoxi, hidroxi, alquilhidroxi, carbonilo, $-CH(OH)CH_3$, $-CH_2NH$-alquil-OH, alquil-$(OH)CH_3$, $-CH_2$-fenil-$(OCH_3)_2$, -Oalquilo, $-OCH_3$, -Ofenilo, -OCOalquilo, -NHCHO, -Nalquilo, -N-(alquil)-CHO, -NH-CO-amino, -N-(alquil)-CO-amino, -NH-COalquilo, -N-(alquil)-COalquilo, -carboxi, -amidino, -CO-amino, -CO-alquilo, $-CO_2$alquilo, mercapto, -Salquilo, $-SCH_2$furanilo, -SO(alquil), $-SO_2$(alquil), $-SO_2$- amino, -alquilsulfonilamino, fenilo, anisol, dimetoxifenilo, trimetoxifenilo, halofenilo, cicloalquilo, heterociclilo, -alquil-NH-cicloalquilo, -alquil-NH-heterociclilo, -alquil-NH-alquil-OH, $-C(=O)OC(CH_3)_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, -alquil-NH-alquil-heterociclilo, -alquil-arilo, -metil-fenilo, alquil-policiclilo, alquil-amino, alquil-hidroxi, $-CH_2NH$-alquil-heterociclilo, $-CH_2NHCH_2CH(CH_3)_2$, vicinal -O(alquil)O-, vicinal -OC(haloalquil)O-, vicinal $-CH_2O$(alquil)O-, vicinal -S(alquil)S- y -O(alquil)S-.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^1 es un heterociclilo opcionalmente

sustituido en donde 1, 2, ó 3 sustituyentes se selecciona/seleccionan de: -OH, $C(=O)OC(CH_3)_3$, NH_2, C_{1-6}alquilo, metoxibenceno, o dimetoxibenceno.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^1 es un heterociclilo, en donde heterociclilo se selecciona de piperdinilo, piridinilo, pirrolidinilo, pirazinilo, azepanilo, azetidinilo, azabiciclozinilo, furanilo, tienilo.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^2 es H.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^4 es H.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^5 es H o un C_{1-6}alquilo opcionalmente sustituido.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^5 es H un C_{1-6}alquilo opcionalmente sustituido donde 1, 2 ó 3 sustituyentes se selecciona/seleccionan de: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH_3, OH, -C_{1-6}alquilo, morfolino, piperidinilo, pirrolodinilo.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor

hidrolizable *in vivo* en donde R^5 es H o un C_{1-3}alquilo opcionalmente sustituido.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde R^5 es H o un C_{1-3}alquilo opcionalmente sustituido en donde 1, 2 ó 3 sustituyentes se selecciona/seleccionan de: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH_3, OH, -C_{1-6}alquilo, morfolino, piperidinilo, pirrolodinilo.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde

R^1 es un heterociclilo opcionalmente sustituido;

R^2 es H;

R^4 es H;

R^5 es H o un C_{1-6}alquilo opcionalmente sustituido.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde:

R^1 es un heterociclilo opcionalmente sustituido en donde el sustituyente se selecciona de uno o más de los siguientes: -NH_2, C_{1-6}alquilo, -$C(=O)OC(CH_3)_3$,

R^2 es H;

R^4 es H;

R^5 es H o un C_{1-6}alquilo opcionalmente sustituido en donde el sustituyente se selecciona de uno o más de los siguientes: -C_{1-6}alquilo, -$N(C_{1-3}alquil)_2$.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde:

R^1 es un heterociclilo opcionalmente sustituido en donde el sustituyente se selecciona de uno o más de los siguientes: $-NH_2$,C_{1-6}alquilo, $-C(=O)OC(CH_3)_3$,

R^2 es H;

R^4 es H;

R^5 es H o un C_{1-3}alquilo opcionalmente sustituido en donde 1, 2 ó 3 sustituyentes se selecciona/seleccionan de: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH_3, OH, $-C_{1-6}$alquilo, morfolino, piperidinilo, pirrolodinilo.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde:

R^1 es un heterociclilo;

R^2 es H;

R^4 es H;

R^5 es H o un C_{1-6}alquilo.

Una incorporación de la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en donde:

R^1 es un heterociclilo de 6 miembros que contiene por lo menos un N en el anillo;

R^2 es H;

R^4 es H;

R^5 es un C_{1-3}alquilo.

Una incorporación de la presente invención provee compuestos de fórmula (I) seleccionados de los siguientes:

terc-butil 3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;

terc-butil 3-{[(2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[(3R)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida;

N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{4-[2-(dietilamino)etoxi]fenil}-2-tienil)urea;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(2-aminoetil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1-metilpiperidin-4-il)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilazepan-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilpiperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-pirrolidin-3-il] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[2-(dimetilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[2-(dietilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piperidin-4-ilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-pirrolidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(1-etilpiperidin-3-il)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[(3S)-1-etilazepan-3-il]-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(3-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

terc-butil(3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)pirrolidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(1-bencilpiperidin-4-il)-5-(4-metoxifenil) tiofen-3-carboxamida;

terc-butil 3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-azetidin-3-il-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(2S)-pirrolidin-2-ilmetil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piridin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperidin-1-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-1-azabiciclo[2.2.2]oct-3-il-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(2-hidroxietil)-5-(4-hidroxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(trans-4-hidroxiciclohexil)-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2,2,6,6-tetrametilpiperidin-4-il)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(2-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(tetrahidrofuran-2-ilmetil) tiofen-3-carboxamida;

terc-butil (3R)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-3-ilmetil)tiofen-3-carboxamida;-

terc-butil 3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)azetidin-1-carboxilato;

2[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-4-ilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(3-metoxipropil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida;

N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]urea;

2-[(aminocarbonil)amino]-N-(2-metoxietil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-{2-[(2-furilmetil)tio]etil}-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida;

N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{3-[2-(dietilamino)etoxi] fenil}-2-tienil)urea;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1,2,3,4-tetrahidroquinolin-3-il)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(1,3-benzodioxol-5-ilmetil)-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(3-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[2-(3,4-dimetoxifenil)etil]-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(5-metil-2-furil)metil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-2-ilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(4-fluorobencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

terc-butil 4-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-N-(2-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-fenoxietil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-2-iletil)tiofen-3-carboxamida;

terc-butil 4-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-N-(4-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida;

terc-butil(3S)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-{4-[2-(dietilamino)etoxi]fenil}tiofen-3-carboxamida;

terc-butil (3R)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

N-[3-{[(3S)-3-aminoazepan-1-il]carbonil}-5-(4-metoxifenil)-2-tienil]urea;

5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

5-{3-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

N-[(3S)-azepan-3-il]-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida;

5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

N-(2-aminoetil)-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida;

5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

5-(4-metoxifenil)-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida;

terc-butil 3-{[(5-{3-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino) carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea;

N-[3-[(3-aminopirrolidin-1-il)carbonil]-5-(4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea;

terc-butil 4-{[(5-[4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

terc-butil 3-[(5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino) carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

5-[4-(2-dietilamino-etoxi)-fenil]-2-(3-hidroxi-urea)-tiofen-3-ácido carboxílico-(S)-piperidin-3-ilamida;

2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(3-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(2-hidroxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-[2-(benciloxi)fenil]-*N*-[(3S)-piperidin-3-il]tiofen-3-carboxamida.

Una incorporación de la presente invención provee compuestos de fórmula (I) o su sal farmacéuticamente aceptable para uso como un medicamento.

Una incorporación de la presente invención provee compuestos de fórmula (I) o su sal farmacéuticamente aceptable en la manufactura de un medicamento para el tratamiento o profilaxis de trastornos asociados con cáncer.

Una incorporación de la presente invención provee un método para el tratamiento de cáncer, que comprende administrar a un humano una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable.

Una incorporación de la presente invención provee un método para el tratamiento de cáncer de mama, cáncer colorrectal, cáncer ovárico, cáncer de pulmón cáncer (amicrocítico), tumores cerebrales malignos, sarcomas, melanoma y linfoma, administrando un compuesto de fórmula I o su sal farmacéuticamente aceptable.

Cuna incorporación de la presente invención provee un método de tratar cáncer administrando a un humano un compuesto de fórmula (I) o su sal farmacéuticamente aceptable y un agente anti-neoplásico.

Una incorporación de la presente invención provee un método de tratar cáncer administrando a un humano un compuesto de fórmula (I) o su sal farmacéuticamente aceptable y un agente que daña el ADN.

Una incorporación de la presente invención provee un método para el tratamiento de infecciones asociadas con cáncer, que comprende administrar a un anfitrión necesitado de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable.

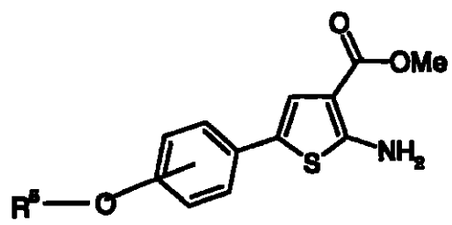
Una incorporación de la presente invención provee un método para el tratamiento profiláctico de infecciones asociadas con cáncer, que

comprende administrar a un anfitrión necesitado de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable.

Una incorporación de la presente invención provee una composición farmacéutica que comprende un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, junto con por lo menos un vehículo, diluyente o excipiente farmacéuticamente aceptable.

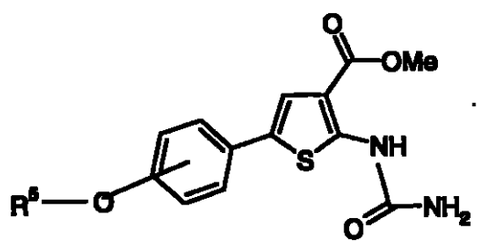
Una incorporación de la presente invención provee un proceso para la preparación de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, que comprende:

(a) la reacción de un 2-aminotiofeno mostrado a continuación como fórmula II



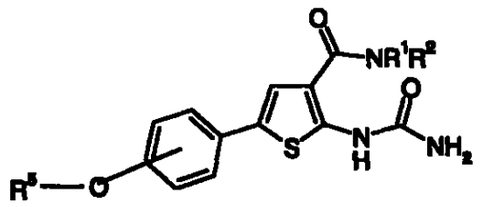
II

en donde el hidrógeno en la posición 2-amino se desplaza para formar una amida, mostrada como fórmula III a continuación:



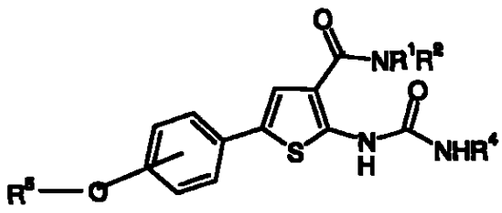
III

en donde el éster de metilo se convierte a una amida utilizando la amina deseada en conjunción con un complejo organometálico de aluminato, para producir el producto mostrado como IV a continuación:



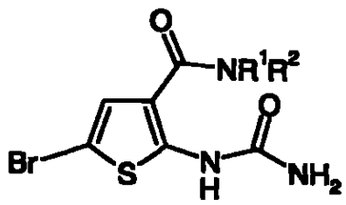
IV

en donde la amida se convierte en varias ureas secundarias sustituidas por la reacción con varios isocianatos para producir el producto mostrado como fórmula V a continuación:



V

Una incorporación de la presente invención provee el uso de un compuesto de fórmula (VI), a continuación, o una sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en la manufactura de un compuesto de fórmula (I).



VI

Las definiciones expuestas en esta solicitud tienen como finalidad aclarar los términos usados de principio a fin de esta solicitud. El término "aquí" significa toda la solicitud.

Tal como se usa en esta solicitud, el término "opcionalmente sustituido," tal como se emplea aquí, significa que la sustitución es opcional y, por lo tanto, es posible que el átomo designado no se sustituya. En el caso que se desee una sustitución, entonces tal sustitución significa que cualquier número de hidrógenos en el átomo designado se reemplaza con una selección del grupo indicado, con la condición que no se exceda la

valencia normal del átomo designado, y que la sustitución tenga como resultado un compuesto estable. Por ejemplo, cuando un sustituyente es ceto (es decir, =O), entonces se reemplazan 2 hidrógenos en el átomo. Ejemplos de tales sustituyentes son los siguientes:
halógeno, nitro, amino, ciano, trifluorometilo, C_{1-6}alquilo, alquenilo, alquinilo, haloalquilo, alcoxi, hidroxi, alquilhidroxi, carbonilo, -$CH(OH)CH_3$, -CH_2NH-alquil-OH, alquil-$(OH)CH_3$, -CH_2-fenil-$(OCH_3)_2$, -Oalquilo, -OCH_3, -Ofenilo, -OCOalquilo, -NHCHO, -N-(alquil)-CHO, -Nalquilo, NH-CO-amino, -N-(alquil)-CO-amino, -NH-COalquilo, -N-(alquil)-COalquilo, -carboxi, -amidino, CO-amino, -CO-alquilo, -CO_2alquilo, mercapto, -Salquilo, -SCH_2furanilo, -SO(alquil), -SO_2(alquil), -SO_2-amino, -alquilsulfonilamino, fenilo, anisol, dimetoxifenilo, trimetoxifenilo, halofenilo, cicloalquilo, heterociclilo, -alquil-NH-cicloalquilo, -alquil-NH-heterociclilo, -alquil-NH-alquil-OH, -$C(=O)OC(CH_3)_3$, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -alquil-NH-alquil-heterociclilo, -alquil-arilo, -metil-fenilo, alquil-policiclilo, alquil-amino, alquil-hidroxi, -CH_2NH-alquil-heterociclilo, -$CH_2NHCH_2CH(CH_3)_2$.

Si la selección se une a un anillo, los sustituyentes podrían seleccionarse asimismo de: vicinal -O(alquil)O-, vicinal-OC (haloalquil)O-, vicinal-CH_2O (alquil)O-, vicinal -S(alquil)S- y -O(alquil)S-.

Una variedad de compuestos en la presente invención pueden existir en formas geométricas o estereoisoméricos particulares. La presente invención toma en cuenta todos aquellos compuestos, incluidos isómeros *cis* y *trans*, R- y S-enantiómeros, diastereómeros, (D)-isómeros, (L)-isómeros, sus mezclas racémicas, y sus otras mezclas, como cubiertos en el ámbito de esta invención. Átomos de carbono asimétricos adicionales pueden estar presentes en un sustituyente tal como un grupo alquilo. Se pretende que todos esos isómeros, así como sus mezclas, se incluyan en esta invención. Los compuestos descritos aquí pueden tener centros asimétricos. Los compuestos de la presente invención, que contienen un átomo

sustituido asimétricamente, pueden aislarse en formas racémicas u óptimamente activas. Es bien conocido en el arte cómo preparar formas óptimamente activas, tal como mediante resolución de formas racémicas o mediante síntesis de materiales de partida óptimamente activos. Si se desea, la separación del material racémico puede lograrse por métodos conocidos en el arte. Muchos isómeros geométricos de olefinas, enlaces dobles C=N y similares pueden estar asimismo presentes en los compuestos descritos aquí, y la totalidad de tales isómeros estables se contempla en la presente invención. Se describen isómeros geométricos *cis* y *trans* de los compuestos de la presente invención y pueden aislarse como una mezcla de isómeros o como formas isoméricas separadas. Se contemplan todas las formas quirales, diastereoméricas, racémicas y todas las formas isoméricas geométricas de una estructura, a menos que se indique expresamente la estereoquímica específica o forma isomérica.

Cuando se muestra que un enlace a un sustituyente cruza un enlace que conecta dos átomos en un anillo, entonces tal sustituyente puede enlazarse a cualquier átomo en el anillo. Cuando un sustituyente se enumera sin indicar el átomo mediante el cual tal sustituyente se enlaza al resto del compuesto de una fórmula dada, entonces tal sustituyente puede enlazarse mediante cualquier átomo en tal sustituyente. Las combinaciones de sustituyentes y/o variables son permisibles únicamente si tales combinaciones resultan en compuestos estables.

Tal como se emplea aquí, "alquilo" o "alquileno" usado solo o como sufijo o prefijo, tiene como finalidad incluir grupos hidrocarburos alifáticos saturados, de cadena recta o ramificada, que tienen de 1 a 12 átomos de carbono o, si se provee un número especificado de átomos de carbono, entonces se consideraría ese número específico. Por ejemplo "C_{1-6} alquilo" denota un alquilo que tiene 1, 2, 3, 4, 5 ó 6 átomos de carbono. Ejemplos de alquilo incluyen, pero no se limitan a, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, sec-butilo, t-butilo, pentilo y hexilo. Tal como se emplea

aquí, "C_{1-3} alquilo", sea un sustituyente terminal o sea un grupo alquileno que enlaza dos sustituyentes, se entiende que incluye específicamente metilo, etilo y propilo de cadena recta y ramificada.

Tal como se emplea aquí, "alquilhidroxi" representa un grupo alquilo de cadena recta o ramificada, como se define más arriba, con el número indicado de átomos de carbono, con uno o más grupos hidroxi unidos. Un ejemplo tal de alquilhidroxi sería $-CH_2OH$.

Tal como se emplea aquí, el término "carbociclilo" tiene como finalidad incluir estructuras de anillo aromático y alicíclico en donde el anillo cerrado se compone de átomos de carbono. Éstas pueden incluir sistemas policíclicos fusionados o en puente. Los carbociclilos pueden tener de 3 a 10 átomos de carbono en su estructura de anillo y, a menudo, tienen 3, 4, 5 y 6 carbonos en la estructura del anillo. Por ejemplo, "C_{3-6}carbociclilo" denota grupos tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopentadieno o fenilo.

Tal como se emplea aquí, el término "cicloalquilo" tiene como finalidad incluir grupos de anillo saturado, que tienen el número especificado de átomos de carbono. Éstos pueden incluir sistemas policíclicos fusionados o en puente. Cicloalquilos preferidos tienen de 3 a 10 átomos de carbono en su estructura de anillo y, más preferiblemente, tienen 3, 4, 5 y 6 carbonos en la estructura del anillo. Por ejemplo, "C_{3-6} cicloalquilo" denota grupos tales como ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo.

Tal como se emplea aquí, "alquenilo" o "alquenileno" tiene como finalidad incluir de 2 a 12 cadenas de hidrocarburo de configuración recta o ramificada con uno o más enlaces dobles carbono-carbono que puedan ocurrir en cualquier punto a lo largo de la cadena. Ejemplos de "C_{3-6}alquenilo" incluyen, pero no se limitan a, 1-propenilo, 2-propenilo, 1-

butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 2-pentenilo, 3-pentenilo, hexenilo.

Tal como se emplea aquí, "alquinilo" o "alquinileno" tiene como finalidad incluir de 2 a 12 cadenas de hidrocarburo de configuración recta o ramificada, con uno o más enlaces triples carbono-carbono, que pueden ocurrir en cualquier punto estable a lo largo de la cadena. Ejemplos de alquinilo incluyen, pero no se limitan a, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo.

Tal como se emplea aquí, el término "alquilcicloalquilo" tiene como finalidad significar un alquilo unido al átomo de la fórmula, modificado con un cicloalquilo. Ejemplos de alquilcicloalquilo incluyen, pero no se limitan a, ciclopropilmetilo, ciclopentilmetilo, ciclohexilmetilo, cicloheptilmetilo, ciclopropiletilo, ciclopentiletilo, ciclohexiletilo, cicloheptiletilo, ciclopropilpropilo, ciclopentilpropilo, ciclohexilpropilo, cicloheptilpropilo.

Tal como se emplea aquí, "cicloalquenilo" se refiere a grupos hidrocarbilo que contienen un anillo, con por lo menos un enlace doble carbono-carbono en el anillo, y con de 3 a 12 átomos de carbono.

Tal como se emplea aquí, "cicloalquinilo" se refiere a grupos hidrocarbilo que contienen un anillo, con por lo menos un enlace triple carbono-carbono en el anillo, y con de 7 a 12 átomos de carbono.

Tal como se emplea aquí, el término "aralquilo" se refiere a un grupo alquilo sustituido con un grupo arilo (un grupo aromático o heteroaromático).

Tal como se emplea aquí, "aromático" se refiere a grupos hidrocarbilo con uno o más anillo de carbono poliinsaturado con carácter aromático

(verbigracia, 4n + 2 electrones deslocalizados) y que comprende hasta alrededor de 14 átomos de carbono.

El término "arilo", tal como se emplea aquí, incluye grupos aromáticos de un solo anillo, de 5, 6 y 7 miembros, que pueden incluir de cero a cuatro heteroátomos, por ejemplo, benceno, furano, imidazol, isoxazol, nicotínico, isonicotínico, oxazol, fenilo, pirazol, pirazina, piridazina, piridina, pirimidina, tiazol, tiofeno, triazol y similares. Aquellos grupos arilo con heteroátomos en la estructura del anillo pueden denominarse también "heteroarilo" o "heteroaromáticos." El anillo aromático puede sustituirse en una o más posiciones de anillo con sustituyentes como se describen más arriba. El término "arilo" incluye asimismo sistemas de anillo policíclico con dos o más anillos cíclicos, en los cuales dos o más carbonos son comunes a los dos anillos contiguos (los anillos son "anillos fusionados") en donde por lo menos uno de los anillos es aromático, por ejemplo, los demás anillos cíclicos pueden ser cicloalquilos, cicloalquenilos, cicloalquinilos, arilos y/o heterociclilos.
Los términos ***orto***, ***meta*** y ***para*** se aplican a bencenos 1,2-, 1,3- y 1,4-disustituidos, respectivamente. Por ejemplo, los nombres 1,2-dimetilbenceno y orto-dimetilbenceno son sinónimos.

Tal como se emplea aquí, el término "heterociclilo" o "heterocíclico" o "heterociclo" se refiere a estructuras monovalentes y divalentes que contienen un anillo, con uno o más heteroátomos, seleccionados independientemente de N, O y S, como parte de la estructura de anillo y que comprenden de 3 a 20 átomos en los anillos, más preferiblemente, anillos de 3 a 7 miembros. Los grupos heterocíclicos pueden ser saturados o insaturados, conteniendo uno o más enlaces dobles, y los grupos heterocíclicos pueden contener más de un anillo, como en el caso de sistemas policíclicos. Los anillos heterocíclicos descritos aquí pueden sustituirse en un átomo de carbono o en un heteroátomo, si el compuesto resultante es estable. Si se anota específicamente, el nitrógeno en el

heterociclil puede, en forma opcional, cuaternizarse. Se entiende que cuando el número total de átomos de S y O en el heterociclilo es superior a 1, entonces estos heteroátomos no son adyacentes unos con otros.

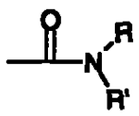
Ejemplos de heterociclilos incluyen, pero no se limitan a, 1H-indazol, 2-pirrolidonilo, 2H, 6H-1, 5,2-ditiazinilo, 2H-pirrolilo, 3H-indolilo, 4-piperidonilo, 4aH-carbazol, 4H-quinolizinilo, 6H-1, 2,5-tiadiazinilo, acridinilo, azabiciclo, azetidina, azepán, aziridina, azocinilo, benzimidazolilo, benzodioxol, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benztiazolilo, benzotriazolilo, benzotetrazolilo, benzisoxazolilo, benzisotiazolilo, benzimidazalonilo, carbazolilo, 4aH-carbazolilo, b-carbolinilo, cromanilo, cromenilo, cinolinilo, diazepán, decahidroquinolinilo, 2H,6H-1,5,2-ditiazinilo, dioxolano, furilo, 2,3-dihidrofurano, 2,5dihidrofurano, dihidrofuro[2,3-b] tetrahidrofurano, furanilo, furazanilo, homopiperidinilo, imidazolidina, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolenilo, indolinilo, indolizinilo, indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, morfolinilo, naftitiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxirano, oxazolidinilperimidinilo, fenantridinilo, fenantrolinilo, fenarsazinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, piperidonilo, 4-piperidonilo, purinilo, piranilo, pirrolidinilo, pirrolina, pirrolidina, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazol, piridoimidazol, piridotiazol, piridinilo, N-óxido-piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolinilo, pirrolilo, piridina, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, carbolinilo, tetrahidrofuranilo, tetrahidroquinolina, tetrahidroisoquinolinilo, tiofano, tiotetrahidroquinolinilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolilo,

tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, tiirano, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo, xantenilo.

Los términos "policiclilo" o "grupo policíclico" se refieren a dos o más anillos (por ejemplo, cicloalquilos, cicloalquenilos, cicloalquinilos, arilos y/o heterociclilos) en los cuales dos o más carbonos son comunes a dos anillos contiguos, por ejemplo, los anillos son "anillos fusionados." Los anillos que se unen mediante átomos no adyacentes se denominan anillos "en puente". Cada uno de los anillos del policiclo puede sustituirse con sustituyentes como los descritos más arriba, como por ejemplo, halógeno, alquilo, aralquilo, alquenilo, alquinilo, cicloalquilo, hidroxilo, amino, nitro, sulfhidrilo, imino, amido, carbonilo, carboxilo, éter, alquiltio, sulfonilo, cetona, aldehído, éster, heterociclilo, una fracción aromática o heteroaromática, $-CF_3$, -CN, o similares. Ejemplos de tales heterociclilos en puente incluyen quinuclidina, diazabiciclo[2.2.1]heptano y 7-oxabiciclo[2.2.1]heptano, piperazina sustituida.

Tal como se emplea aquí, el término "amina" o "amino" se refiere a grupos de la fórmula general -NRR', en donde R y R' se representan cada uno independientemente por, pero no limitados a, hidrógeno, alquilo, cicloalquilo, alquenilo, arilo, heteroarilo, aralquilo, o heteroaralquilo. Ejemplos del grupo amino incluyen, pero no se limitan a, NH_2, metilamina, etilamina, dimetilamina, dietilamina, propilamina, bencilamina y similares.

Tal como se emplea aquí, el término "amido" es reconocido en el arte como un carbonilo amino-sustituido e incluye una fracción que puede representarse por la fórmula general:

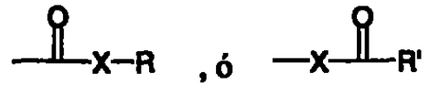


en donde R y R' se representan cada uno independientemente por, pero no se limitan a, hidrógeno, alquilo, cicloalquilo, alquenilo, arilo, heteroarilo, heterociclilo, aralquilo, o heteroaralquilo, o R y R' pueden formar un anillo.

Tal como se emplea aquí, "alcoxi" o "alquiloxi" representa un grupo alquilo, como se define más arriba, con el número indicado de átomos de carbono unidos a través de un puente de oxígeno. Ejemplos de alcoxi incluyen, pero no se limitan a, metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, isobutoxi, t-butoxi, n-pentoxi, isopentoxi, ciclopropilmetoxi, aliloxi y propargiloxi. Análogamente, "alquiltio" o "tioalcoxi" representan un grupo alquilo, como se definen más arriba, con el número indicado de átomos de carbono unidos a través de un puente de azufre.

Tal como se emplea aquí, el término "acilo" se refiere a grupos de la fórmula general-C(=O)-R, en donde R es hidrógeno, un radical hidrocarbilo. Ejemplos de grupos acilo incluyen, pero no se limitan a, acetilo, propionilo, benzoilo, fenilacetilo.

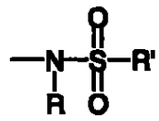
Tal como se emplea aquí, el término "carbonilo" se reconoce en el arte e incluye aquellas fracciones que pueden representarse por la fórmula general:



en donde X es un enlace o representa un oxígeno o azufre, y R representa un hidrógeno, un alquilo, un alquenilo, $-(CH_2)_m-R''$ o una sal farmacéuticamente aceptable, R' representa un hidrógeno, un alquilo, un alquenilo o $-(CH_2)_m-R''$, donde m es un entero menor o igual a diez, y R'' es alquilo, cicloalquilo, alquenilo, arilo, o heteroarilo. Donde X es un oxígeno y R y R' no son hidrógeno, la fórmula representa un "éster". Donde X es un oxígeno, y R es como se define más arriba, la fracción indicada aquí como un grupo carboxilo y, particularmente, cuando R' es un hidrógeno, la fórmula representa un "ácido carboxílico." Donde X es oxígeno, y R' es un

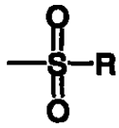
hidrógeno, la fórmula representa un "formiato." En general, donde el átomo de oxígeno de la fórmula anterior se reemplaza por azufre, la fórmula representa un grupo "tiolcarbonilo". Donde X es un azufre y R y R' no es hidrógeno, la fórmula representa "tioléster." Donde X es azufre y R es hidrógeno, la fórmula representa "ácido tiolcarboxílico." Donde X es azufre y R' es hidrógeno, la fórmula representa "tiolformiato." De otro lado, donde X es un enlace, y R no es un hidrógeno, la fórmula anterior representa un grupo "cetona". Donde X es un enlace, y R es hidrógeno, la fórmula anterior representa un grupo "aldehído".

Tal como se emplea aquí, el término "sulfonilamino" es reconocido en el arte y se refiere a una fracción que puede representarse por la fórmula general:



en donde R y R' se representan cada uno independientemente, pero no se limitan a hidrógeno, alquilo, cicloalquilo, alquenilo, arilo, heteroarilo, heterociclilo, aralquilo, o heteroaralquilo.

Tal como se emplea aquí, el término "sulfonilo" se reconoce en el arte y se refiere a una fracción que puede representarse por la fórmula general:



en donde R se representa, pero no se limita a hidrógeno, alquilo, cicloalquilo, alquenilo, arilo, heteroarilo, aralquilo, o heteroaralquilo.

Tal como se emplea aquí, "halo" o "halógeno" se refiere a fluoro, cloro, bromo y yodo. "Ión contrario" se utiliza para representar una especie pequeña, de carga negativa tal como cloruro, bromuro, hidróxido, acetato, sulfato, tosilato, bencenosulfonato y similares.

Tal como se emplea aquí, "haloalquilo" tienen como finalidad incluir grupos hidrocarburo alifático saturado, de cadena recta o ramificada, con el número especificado de átomos de carbono, sustituido con 1 ó más halógenos (por ejemplo-C_vF_w donde v=1 a 3 y w=1 a (2v+1)). Ejemplos de haloalquilo incluyen, pero no se limitan a, trifluorometilo, triclorometilo, pentafluoroetilo, pentacloroetilo, 2,2,2-trifluoroetilo, 2,2-difluoroetilo, heptafluoropropilo y heptacloropropilo. "Haloalcoxi" tiene como finalidad significar un grupo haloalquilo, como se define más arriba, con el número indicado de átomos de carbono unidos mediante un puente de oxígeno; por ejemplo trifluorometoxi, pentafluoroetoxi, 2,2,2-trifluoroetoxi y similares. "Haloalquiltio" tiene como finalidad significar un grupo haloalquilo, como se define más arriba, con el número indicado de átomos de carbono unidos mediante un puente de azufre.

Tal como se emplea aquí, la expresión "grupo protector" significa sustituyentes temporales que protegen un grupo funcional potencialmente reactivo de transformaciones químicas indeseadas. Ejemplos de tales grupos protectores incluyen ésteres de ácidos carboxílicos, silil éteres de alcoholes, y acetales y cetales de aldehídos y cetonas respectivamente. El campo de la química de grupos protectores se ha reseñado (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3^{td} ed.; Wiley: New York, 1999).

Tal como se emplea aquí, "farmacéuticamente aceptable" se emplea aquí para referirse a aquellos compuestos, materiales, composiciones, y/o formulaciones farmacéuticas que, en el ámbito de un juicio médico acertado, son apropiados para uso en contacto con los tejidos de seres humanos y animales sin toxicidad excesiva, irritación, respuesta alérgica, u otro problema o complicación, proporcionado con una relación razonable riesgo/beneficio.

Tal como se emplea aquí, "sales farmacéuticamente aceptables" se refieren a derivados de los compuestos divulgados en donde el compuesto precursor se modifica elaborando sus sales de ácido o base. Ejemplos de sales farmacéuticamente aceptables incluyen, pero no se limitan a, sales ácido orgánico o mineral de residuos básicos, tales como aminas; sales orgánicas o alcalinas de residuos acídicos tales como ácidos carboxílicos; y similares. Las sales farmacéuticamente aceptables incluyen las sales atóxicas convencionales o las sales de amonio cuaternario del compuesto precursor formado, por ejemplo, de ácidos orgánicos o inorgánicos atóxicos. Por ejemplo, tales sales atóxicas convencionales incluyen aquellas derivadas de ácidos inorgánicos tales como ácido clorhídrico, fosfórico y similares; y las sales preparadas de ácidos orgánicos tales como ácido láctico, maleico, cítrico, benzoico, metanosulfónico y similares.

Las sales farmacéuticamente aceptables de la presente invención pueden sintetizarse del compuesto precursor, que contiene una fracción básica o ácida, por métodos químicos convencionales. Generalmente, tales sales pueden prepararse haciendo reaccionar las formas de ácido libre o base de estos compuestos con una cantidad estequiométrica de la base o ácido apropiado en agua o en un disolvente orgánico, o en una mezcla de los dos; generalmente se utilizan medios no acuosos tales como éter, acetato de etilo, etanol, isopropanol, o acetonitrilo.

Tal como se emplea aquí, "éster hidrolizable *in vivo*" significa un éster, susceptible de hidrolizarse (o descomponerse) *in vivo*, de un compuesto de la fórmula (I) que contiene un grupo carboxi o un grupo hidroxi. Por ejemplo ésteres de aminoácidos, ésteres de C_{1-6} alcoximetilo como metoximetilo; ésteres de C_{1-6}alcanoiloximetilo como pivaloiloximetilo; ésteres de C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquilo tales como 1-ciclohexilcarboniloxietilo, acetoximetoxi, o ésteres cíclicos fosforamídicos.

Tal como se emplea aquí "compuesto estable" y "estructura estable" tienen con fin indicar un compuesto lo suficientemente robusto para sobrevivir al aislamiento, en un grado útil de pureza, de una mezcla de reacción, y la formulación en un agente terapéutico eficaz.

El tratamiento anti-cáncer definido aquí puede aplicarse como terapia única o pueden involucrar, aparte del compuesto de la invención, cirugía o radioterapia o quimioterapia convencionales. Tal quimioterapia puede incluir uno o más de las siguientes categorías de agentes antineoplásicos:

(i) medicamentos antiproliferativos/antineoplásicos/que tienen como objetivo la destrucción del ADN y sus combinaciones, como se emplean en la oncología médica, tales como agentes alquilantes (por ejemplo cis-platino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, busulfán y nitrosoureas); antimetabolitos (por ejemplo antifolatos tales como fluoropirimidinas como 5-fluorouracilo y tegafur, raltitrexed, metotrexato, citarabina e hidroxiurea y gemcitabina); antibióticos antineoplásicos (por ejemplo antraciclinas como adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo antineoplásicos como vincristina, vinblastina, vindesina y vinorelbina y taxoides como taxol y taxotero); e inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y tenipósido, amsacrina, topotecán, irinotecán y camptotecina) y agentes citodiferenciadores (por ejemplo, ácido todo-transretinoico y fenretinida);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo tamoxifeno, toremifeno, raloxifeno, droloxifeno y yodoxifeno), reguladores por disminución del receptor de estrógeno (por ejemplo, fulvestrant), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo goserelina, leuprorelina y buserelina), progestógenos (por ejemplo, acetato de megestrol), inhibidores de aromatasa (por ejemplo, anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5α-reductasa tales como finasteride;

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(iii) agentes que inhiben la invasión celular del cáncer (por ejemplo, inhibidores de metaloproteinasa como marimastat e inhibidores de la función de receptor activador de plasminógeno tipo urocinasa);

(iv) inhibidores de la función de factor de crecimiento, por ejemplo tales inhibidores incluyen anticuerpos de factor de crecimiento, anticuerpos de receptor de factor de crecimiento, (por ejemplo el anticuerpo anti-erbb2 trastuzumab [Herceptin™] y el anticuerpo anti-erbb1 cetuximab [C225]), inhibidores de farnesiltransferasa, inhibidores de tirosina cinasa e inhibidores de serina/treonina cinasa, por ejemplo inhibidores de la familia de factor de crecimiento epidérmico (por ejemplo inhibidores de la tirosina cinasa de la familia EGFR tales como N-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, AZD1839), N-(3-etinilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina (erlotinib, OSI-774) y 6-acrilamido-N-(3-cloro-4-fluorofenil)-7-(3-morfolinopropoxi)quinazolin-4-amina (CI 1033)),por ejemplo inhibidores de la familia de factor de crecimiento derivado de plaquetas y, por ejemplo, inhibidores de la familia de factor de crecimiento de hepatocitos;

(v) agentes antiangiogénicos tales como aquellos que inhiben los efectos del factor de crecimiento endotelial vascular, (por ejemplo el anticuerpo de factor de crecimiento celular endotelial anti-vascular bevacizumab [Avastin™], compuestos como los divulgados en las Solicitudes Internacionales de Patentes WO 97/22596, WO 97/30035, WO 97/32856 y WO 98/13354) y compuestos que funcionan por otros mecanismos (por ejemplo linomide, inhibidores de la función integrina αvβ3 y angiostatina)

(vi) agentes de lesión vascular tales como combretastatina A4 y compuestos divulgados en las Solicitudes Internacionales de Patente WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) genoterapias que pueden desacelerar o detener el crecimiento de células cancerosas (***"antisense therapies"***), por ejemplo aquellas que se dirigen a los objetivos enumerados más arriba, tales como ISIS 2503, una genoterapia

anti-ras;

(viii) métodos de genoterapia, incluidos por ejemplo, métodos para reemplazar genes aberrantes tales como p53 aberrante o BRCA1 aberrante o métodos BRCA2, GDEPT (terapia con profármacos enzimáticos direccionados por genes) tales como los que usan deaminasa de citosina, cinasa de timidina o una enzima nitrorreductasa bacteriana y métodos para aumentar la tolerancia del paciente a la quimioterapia o la radioterapia tales como genoterapias de resistencia multi-fármaco; y

(ix) métodos de inmunoterapia, incluidos por ejemplo métodos *ex-vivo* e *in-vivo* para aumentar la inmunogenicidad de células tumorales en el paciente, tales como transfección con citocinas tales como interleucina 2, interleucina 4 o factor estimulante de colonias macrófago-granulocito, métodos para disminuir la anergia de células T, métodos que utilizan células inmunes transfectadas tales como células dendríticas transfectadas con citocina, métodos que utilizan estirpes de células tumorales transfectadas con citosina y métodos que utilizan anticuerpos anti-idiopáticos.

Tal tratamiento conjunto puede lograrse mediante la administración simultánea, consecutiva o separada de los componentes individuales del tratamiento. Tales productos de combinación emplean los compuestos de esta invención.

Los compuestos de la presente invención pueden administrarse por vía oral, parenteral, bucal, vaginal, rectal, por inhalación, insuflación, sublingual, intramuscular, subcutánea, local, intranasal, intraperitoneal, intratorácica, intravenosa, epidural, intratecal, intracerebroventricular y por inyección en las articulaciones.

La medicación dependerá de la vía de administración, la gravedad de la enfermedad, la edad y el peso del paciente y otros factores considerados normalmente por el médico residente, al determinar el régimen individual y el nivel posológico como el más apropiado para un paciente particular.

Una cantidad efectiva de un compuesto de la presente invención para uso en la terapia de la infección es una cantidad suficiente para aliviar de manera indicativa en un animal de sangre caliente, particularmente un

humano, los síntomas de infección, para desacelerar la evolución de la infección, para reducir, en pacientes con síntomas de infección, el riesgo de empeorar.

Para preparar composiciones farmacéuticas de los compuestos de esta invención, excipientes inertes, farmacéuticamente aceptables, pueden ser sólidos o líquidos. Preparaciones en forma sólida incluyen polvos, tabletas, gránulos dispersables, cápsulas, sellos, y supositorios.

Un excipiente sólido puede ser una o más sustancias, que pueden actuar también como diluyentes, saborizantes, solubilizantes, lubricantes, agentes de suspensión, aglutinantes, o agentes desagregantes de tabletas; puede ser asimismo un material encapsulante.

En polvos, el excipiente es un sólido finamente dividido, que se encuentra mezclado con el componente activo finamente dividido. En tabletas, el componente activo se mezcla con el excipiente que tiene las propiedades aglutinantes necesarias en proporciones adecuadas y se compacta en la forma y el tamaño deseados.

Para preparar composiciones de supositorio, primeramente se funde una cera de baja fusión tal como una mezcla de glicéridos de ácido graso y manteca de cacao, y el ingrediente activo se dispersa en ella mediante agitación, por ejemplo. La mezcla homogénea fundida se vierte entonces en moldes de tamaño conveniente y se deja enfriar y solidificar.

Excipientes apropiados incluyen carbonato de magnesio, estearato de magnesio, talco, lactosa, azúcar, pectina, dextrina, almidón, tragacanto, metilcelulosa, carboximetilcelulosa sódica, una cera con bajo punto de fusión, manteca de cacao, y similares.

Algunos de los compuestos de la presente invención son capaces de formar sales con varios ácidos y bases, orgánicos e inorgánicos, y tales sales se encuentran también dentro del ámbito de esta invención. Por ejemplo, tales sales atóxicas convencionales incluyen aquellas derivadas de ácidos inorgánicos, tales como ácido clorhídrico, fosfórico y similares; y las sales preparadas de ácidos orgánicos tales como ácido láctico, maleico, cítrico, benzoico, metanosulfónico, trifluoroacetato y similares.

En una incorporación un compuesto de la fórmula (I) o su sal farmacéuticamente aceptable para el tratamiento terapéutico (incluido el tratamiento profiláctico) de mamíferos, inclusive humanos, se formula normalmente de acuerdo con la práctica farmacéutica estándar como un composición farmacéutica.

Además de los compuestos de la presente invención, la composición farmacéutica de esta invención puede contener asimismo, o co-administrarse (simultánea o secuencialmente), con uno o más agentes farmacológicos de utilidad en el tratamiento de una o más condiciones patológicas mencionadas aquí.

El término composición tiene como finalidad incluir la formulación del componente activo o una sal farmacéuticamente aceptable con un excipiente farmacéuticamente aceptable. Por ejemplo, esta invención puede formularse por medios conocidos en el arte en la forma de, por ejemplo, tabletas, cápsulas, soluciones acuosas u oleosas, suspensiones, emulsiones, cremas, ungüentos, geles, aerosoles nasales, supositorios, polvos finamente divididos o aerosoles o nebulizadores para inhalación, y para uso parenteral (incluido intravenoso, intramuscular o infusión) soluciones estériles oleosas o acuosas o suspensiones o emulsiones estériles.

Composiciones de forma líquida incluyen soluciones, suspensiones, y emulsiones. Soluciones estériles de agua-propilenglicol de los compuestos activos pueden mencionarse como un ejemplo de preparaciones líquidas apropiadas para administración parenteral. Composiciones líquidas pueden formularse también en solución en solución acuosa de polietilenglicol. Soluciones acuosas para administración oral pueden prepararse disolviendo el componente activo en agua y añadiendo colorantes apropiados, agentes saborizantes, estabilizantes, y agentes espesantes como se desee. Suspensiones acuosas para uso oral pueden elaborarse dispersando el componente activo finamente dividido en agua junto con un material viscoso tal como gomas naturales/sintéticas, resinas, metilceluosa, caboximetilcelulosa sódica, y otros agentes de suspensión conocidos por el arte de la formulación farmacéutica.

Las composiciones farmacéuticas pueden estar en presentación farmacéutica unitaria. En tal forma, la composición se divide en dosis unitarias que contienen cantidades apropiadas del componente activo. Esta forma farmacéutica unitaria puede ser una preparación empacada, conteniendo el paquete cantidades discretas de las preparaciones, por ejemplo, tabletas empacadas, cápsulas, y polvos en frasquitos o ampolletas. La forma farmacéutica unitaria, puede ser además una cápsula, sello, o tableta en sí, o puede ser el número apropiado de cualquiera de estas formas empacadas.

Los compuestos de fórmula (I) han demostrado que inhiben la actividad cinasa de punto de control *in vitro*. Los inhibidores de cinasa de punto de control han demostrado que permiten a las células avanzar inapropiadamente a la metafase de la mitosis conduciendo a la apoptosis de las células afectadas y, por lo tanto, poseen efectos anti-proliferativos. Por consiguiente, se cree que los compuestos de fórmula (I) pueden usarse para el tratamiento de enfermedad neoplásica. Por lo tanto, se espera que los compuestos de fórmula (I) y sus sales sean activos contra enfermedad neoplásica tal como carcinoma del cerebro, mama, ovario, pulmón, colon, próstata, piel u otros tejidos, así como leucemias y linfomas, tumores del sistema nervioso central y periférico, y otros tipos de tumores tales como melanoma, sarcomas, fibrosarcoma y osteosarcoma. Adicionalmente, se espera también que los compuestos de fórmula (I) sean útiles para el tratamiento de otras enfermedades proliferativas. Se espera que los compuestos de fórmula (I) se usen muy probablemente en combinación con una amplia gama de agentes que tienen como objetivo la destrucción del ADN, pero podrían usarse también como agente individual.

Generalmente, los compuestos de fórmula (I) se han identificado en uno o ambos análisis descritos a continuación por tener un valor IC_{50} de 100 micromolares o menos. Por ejemplo, el compuesto de Ejemplo 2 tiene un valor IC_{50} de 10 nM.

Análisis de Cinasa 1 de Punto de Control: Este análisis *in vitro* mide la inhibición de cinasa CHK1 por compuestos. El dominio de cinasa se

expresa en baculovirus y se purifica por la etiqueta GST (*"GST tag"*). A continuación se usa proteína purificada y sustrato de péptido biotinilado (Cdc25C) en un Análisis de Proximidad con Escintilación automatizada de 384 pocillos (*"384 well automated Scintillation Proximity Assay"*) (SPA). Específicamente, péptido, enzima y tampón de reacción se mezclan y dividen en alícuotas en una placa de 384 pocillos que contiene series de dilución de compuestos y controles. Seguidamente se agregan ATP frío y caliente para iniciar la reacción. Luego de 2 horas, se añaden una suspensión de microcápsulas SPA (*"a SPA bead slurry"*), CsCl2 y EDTA para detener la reacción y capturar el péptido biotinilado. Seguidamente las placas se cuentan en un Topcount. Los datos se analizan y se determinan las IC_{50}s para los compuestos individuales.

Análisis de Supresión: Este análisis celular mide la capacidad de inhibidores de CHK1 para suprimir el punto de control G2/M inducido por el daño al ADN. Compuestos activos contra la enzima (< 2 uM) se valoran en el análisis celular. En resumen, células HT29 (estirpe celular de cáncer del colon, p53 invalidado) se esparcen en placas de 96 pocillos el día 1. Al día siguiente, las células se tratan con camptotecina durante 2 horas para inducir el daño del ADN. Luego de 2 horas, se retira la camptotecina y las células se tratan durante 18 horas más con compuesto de prueba y nocodazol, un veneno del huso mitótico (*"a spindle poison"*) que se atrapa en las células en mitosis, que suprime el punto de control. Las células se fijan luego con formaldehído, se tiñen para detectar la presencia de fosfohistona H3, un marcador específico de mitosis, y se etiquetan con tintura Hoechst, de modo que se pueda medir el número de células. Se exploran las placas utilizando el protocolo de Índice Mitótico en el Array Scan (Cellomics). Como control positivo de supresión se usan 4 mM de cafeína.

Los compuestos se prueban en una respuesta a la dosis de 12 puntos en triplicado. Los datos se analizan y se determinan las EC_{50}s para los compuestos individuales.

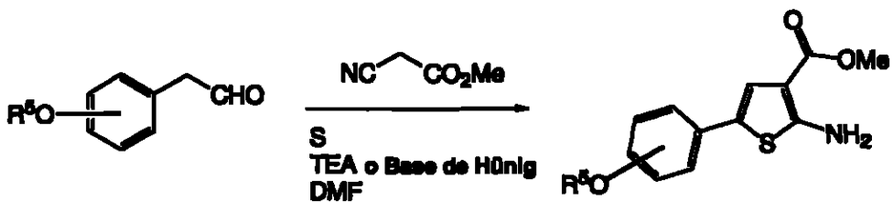
Los compuestos de la presente invención pueden prepararse en un número de maneras bien conocidas por un experto en el arte de la síntesis orgánica. Los compuestos de la presente invención pueden sintetizarse usando los métodos descritos a continuación, junto con métodos sintéticos conocidos en el arte de la química orgánica sintética, o variaciones de los mismos, como se observa por los expertos en el arte. Tales métodos incluyen, pero no se limitan a, los descritos a continuación. Todas las referencias citadas aquí se incorporan en su totalidad por referencia.

Los novedosos compuestos de esta invención pueden prepararse usando las reacciones y técnicas descritas aquí. Las reacciones se llevan a cabo en disolventes apropiados a los reactivos y materiales empleados y son adecuados para las transformaciones que se están efectuando. Además, en la descripción de los métodos sintéticos descritos más adelante, hay que entender que todas las condiciones propuestas, incluidas la elección del disolvente, atmósfera de reacción, temperatura de reacción, duración del experimento y procedimientos de preparación, se eligen como las condiciones estándar para esa reacción, las cuales deberían reconocerse fácilmente por un experto en el arte. Se entiende por un experto en el arte de la síntesis orgánica que la funcionalidad presente en varias porciones de la molécula tiene que ser compatible con los reactivos y reacciones propuestas. Tales restricciones a los sustituyentes, que no sean compatibles con las condiciones de reacción, serán fácilmente evidentes a un experto en el arte, y entonces, tienen que usarse métodos alternos.

Los materiales de partida para los ejemplos contenidos aquí se encuentran disponibles comercialmente o se preparan fácilmente por métodos estándar a partir de materiales conocidos. Por ejemplo, las siguientes reacciones son ilustraciones, no limitaciones de la preparación de algunos de los materiales de partida y los ejemplos usados aquí.

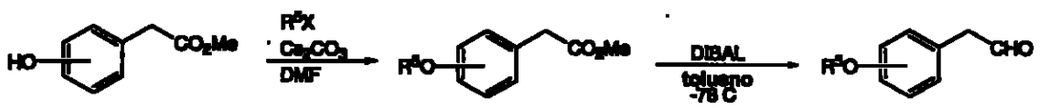
Procedimientos generales para elaborar los compuestos de la invención son los siguientes:

El primero de estos procedimientos se inicia a partir de un intermedio común. Este intermedio núcleo 2- aminotiofeno se produce por síntesis general y simultánea de Gewald (***"a one-pot Gewald synthesis"***) a partir de la reacción de cianometilacetato con varios benzaldehídos y azufre elemental bajo condiciones básicas mostradas a continuación en Esquema I.



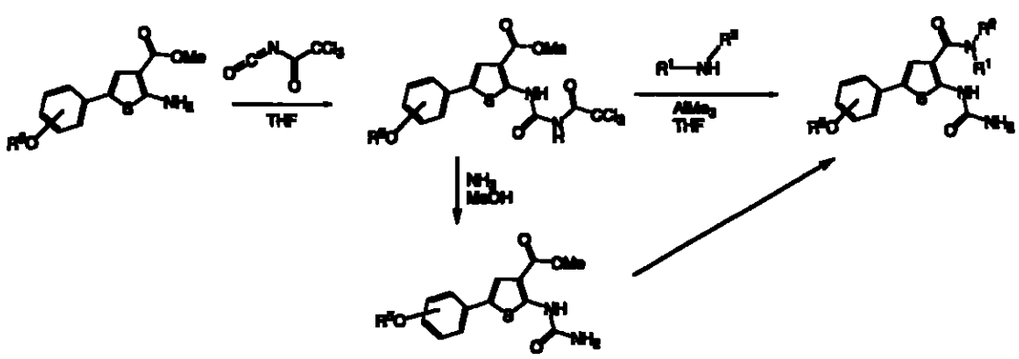
Esquema I

Si no disponibles en el comercio, los correspondientes benzaldehídos podrían sintetizarse usando algunas o todas las transformaciones descritas en Esquema II.



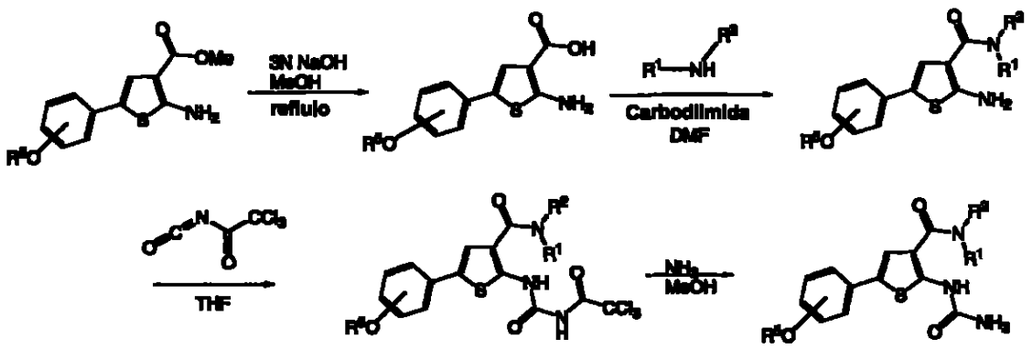
Esquema II

Compuestos de fórmula (I) pueden sintetizarse entonces de los métodos sintéticos generales descritos a continuación en los Esquemas III-IX. El primer método general mostrado en Esquema III involucra una formación de amida de Weinreb a partir de la reacción de la urea, protegida con tricloroacetilo, o urea libre con un complejo organometálico de aminoaluminato.



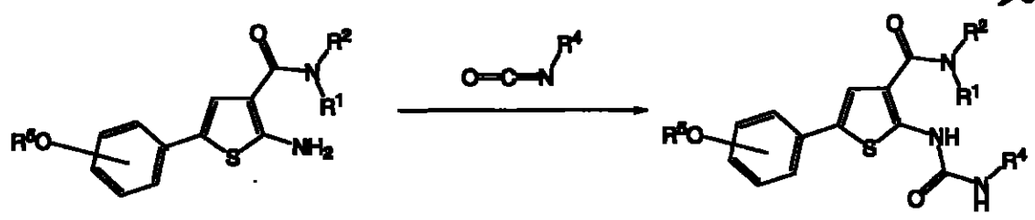
Esquema III

Un método alterno para la generación de compuestos similares se describe en Esquema IV. Esta ruta general utiliza el mismo éster de partida 2-aminotiofeno del Esquema III, pero la formación del enlace amida se ejecuta a partir de la reacción de los ácidos carboxílicos correspondientes con varias aminas. Una variedad de agentes de acoplamiento puede utilizarse para realizar esta transformación incluidos EDCI, DIC, BOP, y HATU bajo métodos de acoplamiento estándar muy familiares a los expertos con práctica y capacitación en el arte de la síntesis orgánica. La generación de la urea primaria final se lleva a cabo entonces usando una sencilla reacción de dos pasos con tricloroacetilisocianato seguida por descomposición con amoníaco en metanol.

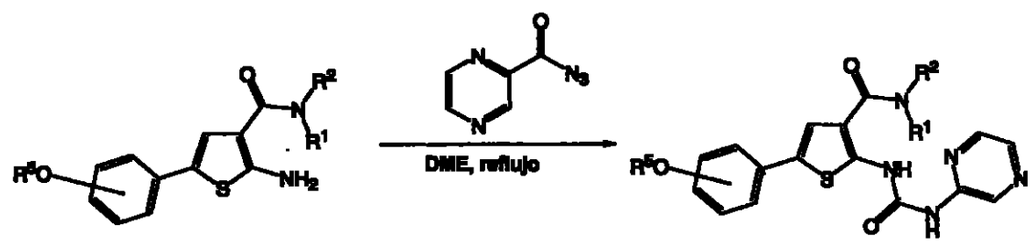


Esquema IV

Como se muestra en los siguientes Esquemas V-VII, el producto amida formado antes de la generación de la urea en Esquema IV puede usarse como intermedio común para la formación de varias ureas sustituidas donde R^4 no es hidrógeno. La reacción con isocianantos, azidas de acilo (en particular, azidas de acilo pirazina), o carbonildiimidazol y aminas (en particular, hidroxilamina clorhidrato), lleva a la creación de varias ureas secundarias sustituidas donde R^4 se selecciona de OH, carbociclilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido.



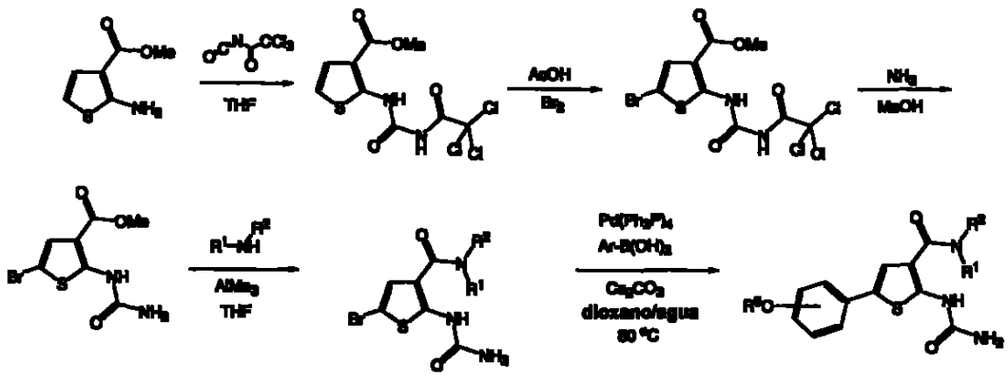
Esquema V



Esquema VI

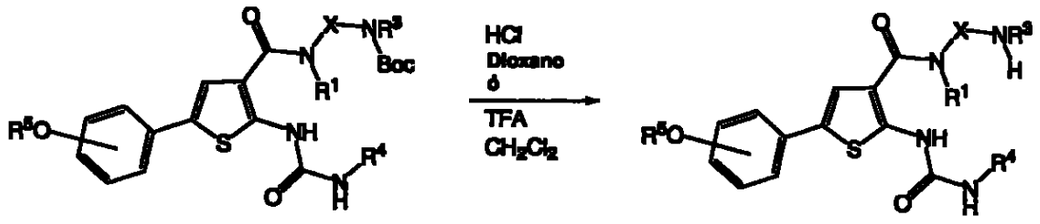
Esquema VII

Un proceso general adicional presentado en esta invención involucra una mejora en la construcción de compuestos generales con fórmula (I). El método, que emplea un acoplamiento de Suzuki de un intermedio 5-bromotiofeno como su transformación clave, se muestra en Esquema VIII. Este método posibilita una diversidad incrementada mucho después en las síntesis y es adaptable a métodos combinatorios paralelos de síntesis orgánicas. Éster metílico de ácido 2-amino-tiofen-3-carboxílico disponible en el comercio se protege como la urea de tricloroacetilo, seguida por bromación selectiva en la posición 5 con bromo y ácido acético. El retiro del grupo protector con amoníaco en metanol, seguida por amidación de Weinreb produce el intermedio común. Condiciones estándar de reacción de Suzuki se emplean entonces para, finalmente, generar los compuestos objetivo.



Esquema VIII

Si el compuesto final generado a partir de cualquiera de los métodos o esquemas ya mencionados tiene un grupo protector en nitrógeno (en particular, un carbamato) u oxígeno (en particular, un éter o éster) presente en cualquier punto en de la molécula, pueden utilizarse métodos estándar de retiro para generar compuestos finales. En Esquema IX se muestra el método general usado para la desprotección de *terc*-butoxicarbonil carbamato para producir el producto de amina secundaria (R^2=XNHR^3) como el correspondiente clorhidrato o sal de trifluoroacetato. La descomposición de éteres de metilo a fenoles (no mostrados) se efectúa por reacción con tribromuro de boro en cloruro de metileno. Estos dos métodos son muy familiares a los expertos entrenados en el arte de la síntesis orgánica.



Esquema IX

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Ejemplos:

Tabla 1

Designación de la IUPAC	Ej.	LCMS (M+1, ES o detección APCI)	^{1}H NMR (d_6-DMSO salvo que se indique lo contrario)	Método de Síntesis (Esquema)
terc-butil 3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-3-tienil)carbonil]amino} piperidin-1-carboxilato trifluoroacetato	1	560	MeOD; 7.55 (d, 2H), 7.45 (s, 1H), 7.05 (d, 2H), 4.35 (m, 2H), 3.90 (m, 3H), 3.60 (m, 2H), 3.30 (m, 4H), 2.95 (dd, 2H), 1.50 (m, 2H), 1.40 (s, 9H), 1.35 (t, 6H)	III
2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida trifluoroacetato	2	460		III
2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino) etoxi]fenil}-N- piperidin-3-iltiofen-3-carboxamida trifluoroacetato	3	460		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-piperidin-3-il] tiofen-3-carboxamida	4	375	1.76-1. 49 (m, 2H), 1.93 (brs, 2H), 2.85 (t, 2H), 3.16 (s, 1H), 3.22(brd, 1H), 3.31 (brd, 1H), 3.77 (s, 3H), 4.11 (brs, 1H), 6.97 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J-8.59 Hz), 7.58 (s, 1H), 8.02 (d, 1H), J=7.33 Hz), 8.65 (brs, 2H), 10.81 (s, 1H)	III
terc-butil 3-{[(2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino) etoxi]fenil}-3-tienil)carbonil]amino} piperidin-1-carboxilato trifluoroacetato	5	560	MeOD; 7.65 (d, 1H), 7.30 (dd, 2H), 7.20 (s, 1H), 6.90 (d, 1H), 4.35 (m, 2H), 3.90 (m, 2H), 3.60 (m, 2H), 3.30 (m, 4H), 3.00 (m, 2H), 2.10 (m, 1H), 1.80 (m, 1H), 1.50 (m, 2H), 1. 45 (s, 9H), 1. 40 (t, 6H)	III
2-[(aminocarbonil)amino]-5-{4-[2-(dletilamino) etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida	6	460	MeOD; 7.52(d, 2H), 7.49(s, 1H), 7.01(d, 2H), 4.35(m, 2H), 3.60 (m,2H), 3.48(m, 1H), 3.42(m, 2H), 3.33(q, 4H), 3.13(m, 2H), 2.14(m, 2H), 1.85 (m,2H), 1.35(t,6H)	III

2-[(aminocarbonil)amino]-N-[(3R)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida	7	389	CDCI3;11.30(brs, 1H), 7.50 (d,2H), 7.05(d, 1H), 7.00(s, 1H), 6.85(d,2H), 5.15(s,2H), 4.20(m, 1H), 3.80(s, 3H), 3.10 (m, 1H), 3.00 (m, 2H), 2.80 (m, 1H), 1.80(m, 2H), 1.70(m, 3H), 1.50 (m, 1H)	III
N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{4-[2-(dietilamino)etoxi]fenil}-2-tienil)urea trifluoroacetato	8	460	MeOD; 7.43(d, 2H), 6.93(d, 2H), 6.92(s, 1H), 4.33(m, 2H), 4.27(dd, 2H), 3.52(dd, 2H), 3.32(m, 1H), 3.24(q, 4H), 3.02(m, 2H), 1.99(m, 1H), 1.95(m, 1H), 1.47(m, 2H), 1.27(t, 6H)	III
2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida trifluoroacetato (sal)	9	483	MeOD; 7.61 (m, 1H), 7.57(s, 1H), 7.49(m, 1H), 7.47(d, 2H), 7.23(t, 1H), 7.03(dd, 1H), 6.93(d, 2H), 4.52(s, 2H), 4.27 (dd, 2H), 4.31(dd, 2H), 3.24(q, 4H), 1.27(t, 6H)	III
2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino) etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida trifluoroacetato	10	460	MeOD; 7.62(s, 1H), 7.29(dd, 1H), 7.24(m, 1H), 7.13(m, 1H), 6.87(m, 1H), 4.35(dd, 2H), 3.59(dd, 2H), 3.46(m, 1H), 3.40(m, 2H), 3.31(q, 4H), 3.10(m, 2H), 2.16(m, 2H), 1.83(m, 2H), 1.34(t, 6H)	III
2-[(aminocarbonil)amino]-N-(2-aminoetil)-5-(4-metoxifenil)tiofen-3-carboxamida	11	335	MeOD; 7.38(d, 2H), 7.36(s, 1H), 6.82(d, 2H), 3.70(s, 3H), 3.57(dd, 2H), 3.10(dd, 2H),	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida	12	375	1.70 (m, 2H), 1.99 (d,2H, J=12.88 Hz), 3.01 (q, 2H, J=11.03 Hz), 3.35 (d, 2H, J=12.38 Hz), 3.76 (s, 3H), 4.01 (brs, 1H), 6.97 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.84 Hz), 7.63 (s, 1H), 8.04 (d, 1H, J=7.07 Hz), 8.43 (d, 1H, J=9.10 Hz), 8.65 (d, 1H, J=8.59 Hz), 10.91 (s, 1H)	III
2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)	13	454	MeOD; 9.51 (s, 1H), 8.75(d, 1H) 8.51 (m,	III

etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida trifluoroacetato			1H), 7.97(s, 1H), 7.93(m, 1H), 7.35(t, 1H), 7.29(m, 2H), 6.93(m, 1H), 4.45(dd, 2H), 3.67(dd, 2H), 3.39(q, 4H), 1.42(t, 6H)	
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1-metilpiperidin-4-il)tiofen-3-carboxamida	14	389	1.76(q, 2H), 2.04(d, 2H, J=12.38 Hz), 2.77 (brd, 3H), 3.08 (q, 2H), 3.48 (d, 2H, J=11.62 Hz), 3.76 (s, 3H), 3.96 (m, 1H), 6.97 (d, 2H), 7.45 (d, 2H, J=8.84 Hz), 7.63 (s, 1H), 8.07 (d, 1H, J=7.33 Hz), 9.62 (brs, 1H), 10.91 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilazepan-3-il] tiofen-3-carboxamida clorhidrato	15	403	CDCl3; 11.35(brs, 1H), 7.50 (d, 2H), 7.15(d, 1H), 6.95(s, 1H), 6.90(d, 2H), 5.30(s, 2H), 4.20(m, 1H), 3.80(s, 3H), 2.85 (m, 1H), 2.80 (d, 1H), 2.60 (dd, 1H), 2.40(m, 1H), 2.45(s, 3H), 1.50-2.00 (m, 6H)	III
2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino) etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida trifluoroacetato (sal)	16	483	MeOD; 7.84(s, 1H), 7.75(m, 1H), 7.63(dd, 1H), 7.35(t, 2H), 7.32(m, 1H), 7.22(m, 1H), 7.16(dd, 1H), 6.92(m, 1H), 4.65(s, 2H), 4.41(dd, 2H), 3.63(dd, 2H), 3.37(q, 4H), 1.40(t, 6H)	III
2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida trifluoroacetato	17	446	MeOD; 7.46(d, 2H), 7.16(s, 1H), 6.95(d, 2H), 4.28(dd, 2H), 3.89(m, 3H), 3.70 (m, 2H), 3.53(dd, 2H), 3.28(q, 4H), 2.30(m, 1H), 2.06(m, 1H), 1.29(t, 6H)	III
2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida trifluoroacetato	18	454	MeOD; 9.59(s, 1H), 8.75(d, 1H), 8.56(d, 1H), 8.00(m, 2H), 7.71 (s, 1H), 7.59(d, 2H), 7.07(d, 2H), 4.41(dd, 2H), 3.65(dd, 2H), 3.38(q, 4H), 1.40(t, 6H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilpiperidin-3-il]tiofen-3-carboxamida clorhidrato	19	389	CDCl3; 11.25(br s, 1H), 7.50 (d, 2H), 7.15(s, 1H), 6.85(d, 2H), 6.90(m, 2H), 5.40 (s, 2H), 4.25(m, 1H), 3.80(s, 3H), 2.40-2.80 (m, 4H), 2.30(s, 3H),	III

			2.20(m, 1H), 1.50-1.90 (m, 3H)	
2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino) etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida trifluoroacetato	20	446	MeOD; 7.40(s, 1H), 7.35(dd, 1H), 7.27(dd, 1H), 7.20(s, 1H), 6.93(m, 1H), 4.42(dd, 2H), 4.01(m, 3H), 3.83 (m, 2H), 3.65(dd, 2H), 3.37(q, 4H), 2.44(m, 1H), 2.18(m, 1H), 1.40(t, 6H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil]tiofen-3-carboxamida	21	389	1.22(dd, 1H, J1 =12.38 Hz, J2=2.53Hz), 1.57(d, 1H, J=13.14Hz), 1.78(brt, 2H), 1.95 (brs, 1H), 2.60 (q, 1H, J=11.37), 2.78 (q, 1H, J=10.61 Hz), 3.09 (m, 1H), 3.25 (m, 3H) 3.77 (s, 3H), 6.97 (d, 2H, J=8.59 Hz), 7.44 (d, 2H, J=8.84 Hz), 7.58 (s, 1H), 8.24 (brs, 1H), 8.30 (brt, 1H), 8.57 (brs, 1H), 10.92 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida	22	361		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-pirrolidin-3-il]tiofen-3-carboxamida	23	361		III
2-[(aminocarbonil)amino]-N-[2-(dimetilamino) etil]-5-(4- metoxifenil)tiofen-3-carboxamida	24	363	MeOD; 7.37(d, 2H), 7.35(s, 1H), 6.80(d, 2H), 3.69(s, 3H), 3.64(m, 2H), 3.29(m, 2H), 2.91 (s, 6H)	III
2-[(aminocarbonil)amino]-N-[2-(dietilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida	25	391		III
2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato	26	389	δ 10.9, s, 1H; δ 9.58, brs, 1H; δ 9.29, brs, 1H; δ 8.39, d, 1H; δ 7.82, s, 1H; δ 7.48, d, 2H; δ 6.96, d, 2H; δ 4.36, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.20, m, 2H; δ 3.07, m, 1H; δ 1.98, m, 1H; δ 1.84, m, 4H; δ 1.59, m, 1H	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-il]tiofen-3-	27	375	1.52 (m, 2H), 1.76 (brs, 1H), 1.89 (brs, 1H), 2.61 (m, 2H), 2.99 (t, 1H),	III

carboxamida			3.16 (m, 1H), 3.76 (s, 3H), 3.95 (brs, 1H), 6.97 (d, 2H), 7.46 (d, 2H), 7.61(s, 1H), 7.89 (d, 1H), 10.90 (s, 1H)	
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piperidin-4-ilmetil)tiofen-3-carboxamida	28	389	1.06 (m, 2H), 1.62 (d, 3H, J=10.11 Hz), 2.95 (d, 2H, J=12.13Hz), 3.11(t, 2H, J=5.68 Hz), 3.76 (s, 3H), 6.90 (d, 1H, J=8.59 Hz), 6.96 (d, 2H, J=8.59 Hz), 7.44 (d, 2H, J=8.59 Hz), 7.61 (s, 1H), 8.14 (t, 1H, J=5.43 Hz), 10.99 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-pirrolidin-3-iltiofen-3-carboxamida	29	361	2.02 (brt, 2H, J=5.81 Hz), 2.22 (dd, 2H, J1 =13.52 Hz, J2=6.69 Hz), 3.21 (dd, 1H, J1 =13.77 Hz, J2=6.95Hz), 3.68(brs, 1H), 3.76 (s, 3H), 3.86 (brs, 1H), 6.96 (brm, 2H), 7.28 (brs, 1H), 7.50 (d, 2H, J=8.84 Hz), 8.16 (brs, 1H), 10.31 (s, 1H)	III
2-[(aminocarbonil)amino]-N-(1-etilpiperidin-3-il)-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato	30	403	11.0 (s, 1H), 7.80(d, 1H), 7.65(s, 1H), 7.45(d, 2H), 6.95(d, 2H), 6.90(brs, 2H), 3.90(m, 1H), 3.75(s, 3H), 2.85(dd, 2H), 2.30(m, 2H), 1.80(m, 3H), 1.70(m, 1H), 1.50(m, 1H), 13.0(m, 1H), 1.0(t, 3H)	III
2-[(aminocarbonil)amino]-N-[(3S)-1-etilazepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato	31	417	11.0(s, 1H), 7.75(d, 1H), 7.65(s, 1H), 7.45(d, 2H), 6.95(d, 2H), 6.90(brs, 2H), 4.05(m, 1H), 3.75(s, 3H), 2.75(m, 1H), 2.40-2.70(m, 5H), 1.85(m, 1H), 1.40-1.75(m, 5H), 0.95(t, 3H)	III
2-[(aminocarbonil)amino]-5-(3-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida	32	361		III
2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida	33	361		III
2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-piperidin-4-iltiofen-3-	34	375		III

carboxamida				
terc-butil (3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino) pirrolidin-1-carboxilato	35	481		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-3-iltiofen-3-carboxamida	36	375		III
2-[(aminocarbonil)amino]-N-(1-bencilpiperidin-4-il)-5-(4-metoxifenil)tiofen-3-carboxamida	37	465	1.75 (m, 2H), 2.08 (d, 2H, J=13.39 Hz), 3.10 (m, 2H), 3.43 (d, 2H, J=11.62 Hz), 3.76 (s, 3H), 3.95 (m, 1H), 4.31 (d, 2H, J=4.55 Hz), 6.97 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.59 Hz), 7.49 (brs, 5H, J=2.27 Hz), 7.61 (s, 1H), 8.05(d, 1H, J=6.82Hz) 9.65(brs, 1H), 10.89 (s, 1H)	III
terc-butil 3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino) piperidin-1-carboxilato	38	475	1.39 (s, 9H), 1.46-1.97 (bm, 4H), 2.72 (t, 2H), 3.16 (s, 2H), 3.77 (s, 3H), 6.96 (d, 2H), 7.45 (d, 2H), 7.62 (s, 1H), 7.85 (brs, 1H), 8.77(d, 1H), 10.95 (s, 1H)	III
2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida	39	494		III
2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida	40	451		III
2-[(aminocarbonil)amino]-N-azetidin-3-il-5-(4-metoxifenil)tiofen-3-carboxamida	41	347		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(2S)-pirrolidin-2-ilmetil]tiofen-3-carboxamida	42	375	1.71 (m, 1H), 1.92 (m, 2H), 2.04 (m, 1H), 3.33-3.11 (m, 2H), 3.62-3.45 (m, 2H), 3.76 (s, 3H), 6.97 (d, 2H, J=8.84 Hz), 7.45 d, 2H, J=8.59 Hz), 7.52 (s, 1H), 7.94 (s, 1H), 8.47 (t, 1H, J=5.81 Hz), 8.52 (brs, 1H), 9.15 (brs, 1H), 10.79(s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-	43	369	3.78 (s, 3H), 7.01 (d, 2H), 7.52 (d, 2H), 7.79	III

piridin-4-iltiofen-3-carboxamida			(s, 1H), 8.15 (d, 2H), 8.70 (brs, 2H), 10.62 (s, 1H), 10.68 (brs, 1H)	
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida	44	404	2.06 (m, 4H), 2.34 (brs, 2H), 2.42 (m, 2H), 2.67 (m, 4H), 3.76 (s, 3H), 6.97 (d, 2H, J=8.84 Hz), 7.44 (d, 2H, J=8.59 Hz), 7.55 (s, 1H), 8.10 (t, 1H, J-5.68 Hz), 10.95 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperidin-1 -iletil)tiofen-3-carboxamida	45	403	1.37 (s, 2H), 1.48 (s, 4H), 2.37 (brs, 4H), 2.42 (t, 2H), 3.76 (s, 3H), 6.94 (brs, 1H), 6.97 (d, 2H), 7.44 (d, 2H), 7.56 (t, 2H), 8.11 (t, 1H), 10.96 (s, 1H)	III
2-[(aminocarbonil)amino]-N-1-azabiciclo[2.2.2]oct-3-il-5-(4-metoxifenil)tiofen-3-carboxamida	46	401		III
2-[(aminocarbonil)amino]-N-(2-hidroxietil)-5-(4-hidroxifenil)tiofen-3-carboxamida	48	322	3.06(t, 1H), 3.5(m, 2H), 6.54(bs, 1H), 6.78-6.97(m, 4H), 7.33(m, 2H), 7.49(s, 1H), 8.34(m, 1H), 9.56(s, 1H), 10.94(s, 1H)	III
2-[(aminocarbonil)amino]-N-(trans-4-hidroxiciclohexil)-5-{4-metoxifenil)tiofen-3-carboxamida	49	390	1.10-1.45 (dq, 4H), 1.85 (t, 4H), 3.40 (brs, 1H), 3.71 (brm, 1H), 3.76 (s, 3H), 4.56 (brs, 1H), 6.90 (brs, 1H), 6.96 (d, 2H), 7.45 (d, 2H), 7.62 (s, 1H), 7.81 (d, 1H), 11.03 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida	50	383	3.17 (t, 2H, J=6.44 Hz), 3.64 (m, 2H), 6.77 (d, 2H, J=8.59 Hz), 7.31 (d, 2H, J=8.59 Hz), 7.45 (s, 1H), 7.97(d, 2H, J=6.32 Hz), 8.27 (s, 1H), 8.83 (d, 2H, J=6.06 Hz), 10.79 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1 -iletil)tiofen-3-carboxamida	52	525	1.34-1.58 (m, 2H), 1.75 (t, 2H, J=14.02 Hz), 1.98 (brs, 1H), 2.01 (d, 1H), 2.80 (m, 3H), 3.48 d, 2H, J=8.59 Hz), 3.73 (s, 6H), 3.75 (s, 3H), 6.63 (dd, 2H, J1=8.34 Hz, J2=4.80 Hz), 6.90 (brs, 1H), 6.95 (d, 2H, J=8.59 Hz), 7.21 (t, 2H), 7.45 (d, 2H, J=8.84 Hz),	III

			7.46 (s, 1H), 7.86 (d, 1H, J=7.58 Hz), 11.00 (s, 1H)	
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida	54	397	3.12 (t, 2H), 3.62 (t, 2H), 3.76 (s, 3H), 6.97 (d, 2H), 7.42 (d, 2H), 7.49 (s, 1H), 7.85 (d, 2H), 8.28 (s, 1H), 8.78 (d, 2H), 10.84 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida	55	383	3.17 (t, 2H, J=6.44 Hz), 3.64 (m, 2H), 6.77 (d, 2H, J=8.59 Hz), 7.31 (d, 2H, J=8.59 Hz), 7.45 (s, 1H), 7.97(d, 2H, J=6.32 Hz), 8.27 (s, 1H), 8.83 (d, 2H, J=6.06 Hz), 10.79 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida	56	397	2.99 (t, 2H), 3.55 (m, 2H), 3.76 (s, 3H), 6.97 (d, 2H), 7.42 (d, 2H), 7.50 (s, 1H), 7.76 (m, 1H), 8.16 (d, 1H), 8.25 (s, 1H), 8.65 (s, 1H), 8.69 (s, 1H), 10.85 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2,2,6,6-tetrametilpiperidin-4-il)tiofen-3-carboxamida	58	431	1.44 (s, 12H), 1.63 (t, 2H), 1.95 (d, 2H), 3.76 (s, 3H), 4.34 (brs, 1H), 6.96 (d, 2H), 7.45 (d, 2H), 7.67 (s, 1H), 8.12 (m, 2H), 9.06 (bd, 1H), 10.92 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(2-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida	59	375		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(tetrahidrofuran-2-ilmetil)tiofen-3-carboxamida	60	376	1.52 (m, 1H), 1.77(m, 3H), 3.25(m, 2H), 3.72(m, 1H), 3.71(s, 3H), 3.93(m, 2H), 6.91(bd, 4H, J=8.84Hz), 7.39(d, 2H, J=8.59Hz), 7.59(s, 1H), 8.17(bs, 1H), 10.91(s, 1H)	III
terc-butil (3R)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino)piperidin-1-carboxilato	62	475	1.38 (s, 9H), 1.47-1.99 (brm, 6H), 3.56 (brm, 2H), 3.74 (brm, 1H), 3.76 (s, 3H), 6.96 (d, 2H, J=8.59 Hz), 7.45 (d, 2H, J=8.84 Hz), 7.62 (s, 1H), 7.85 (brs, 1H), 8.77 (d, 1H, J=7.58Hz), 10.96 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-	63	383	3.76 (s, 3H), 4.48 (d, 2H), 6.96 (d, 2H), 7.36	III

(piridin-3-ilmetil)tiofen-3-carboxamida			(dd, 1H), 7.44 (d, 2H), 7.61 (s, 1H), 7.72 (dt, 1H), 8.46 (bdd, 1H), 8.56 (bd, 1H), 8.77 (t, 1H)	
terc-butil 3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino) azetidin-1-carboxilato	64	447	1.39 (s, 9H), 3.77(s, 3H), 3.86 (m, 2H), 4.13 (t, 2H, J=7.83 Hz), 4.61 (m, 1H), 6.97 (d, 2H, J=8.84 Hz), 7.45 (d, 2H, J=8.59 Hz), 7.60 (s, 1H), 8.57 (d, 1H, J=6.82 Hz), 10.82 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-4-ilmetil)tiofen-3-carboxamida	65	383		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(3-metoxipropil)tiofen-3-carboxamida	67	364	1.76 (m, 2H), 3.23 (s, 3H), 3.30 (t, 2H, 3.37 (t, 2H), 3.76 (s, 3H), 6.96 (d, 2H), 7.44 (d, 2H), 7.57 (s, 1H), 8.15 (brs, 1H), 10.97 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida	68	402		III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida	69	388	3.76 (s, 3H), 4.62 (d, 2H), 6.96 (d, 1H), 6.96 (d, 2H), 7.03 (d, 1H), 7.39 (d, 1H), 7.43 (d, 2H), 7.60 (s, 1H), 8.79 (t, 1H), 10.92 (s, 1H)	III
N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]urea	70	375	7.50 d J=8.8 Hz 2H, 7.09 s 1H, 6.95 d J=8.8 Hz 2H, 3.86 s 3H, 1.23-1.35 m 6H.	III
2-[(aminocarbonil)amino]-N-(2-metoxietil)-5-(4-metoxifenil)tiofen-3-carboxamida	71	350	3.27 (s, 3H), 3.37-3.51 (m, 4H), 3.76 (s, 3H), 6.97 (d, 2H), 7.44 (d, 2H), 7.61 (s, 1H), 8.15-8.26 (m, 1H), 10.95 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida	72	374	4.61 (d, 2H, J=5.81 Hz), 6.77 (d, 2H, J=8.59Hz), 6.96(dd, 2H, J1=5.05 Hz, J2=3.54 Hz), 7.02 (d, 1H, J=3.03 Hz), 7.32 (d, 2H, J=8.34 Hz), 7.38 (d, 1H J=5.05 Hz), 7.53 (s, 1H), 8.77 (t, 1H, J=5.81 Hz), 9.53 (s, 1H) 10.89 (s, 1H)	III
2-[(aminocarbonil)amino]-N-{2-[(2-furilmetil)tio]	74	432	2.61 (t, 2H), 2.65 (t, 2H), 3.75 (s, 3H), 3.81	III

etil}-5-(4-metoxifenil)tiofen-3-carboxamida			(d, 2H), 6.29 (d, 1H, J=3.03Hz), 6.38(dd, 1H, J1=3.03 Hz, J2=1.77 Hz), 6.97 (d, 2H, J=8.84 Hz), 7.44 (d, 2H, J=8.84 Hz), 7.55 (s, 1H), 7.57 (brs, 1H), 8.31 (t, 1H, J=5.68 Hz), 9.10(t, 1H, J=4.93Hz), 10.92 (s, 1H)	
2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida	75	388	3.50(m, 2H), 3.80(m, 2H), 6.54(bs, 1H), 6.78-7.34(m, 7H), 7.49(s, 1H), 8.34(m, 1H), 9.56(s, 1H), 10.94(s, 1H)	III
N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{3-[2-(dietilamino)etoxi]fenil}-2-tienil)urea trifluoroacetato	76	460	MeOD; 7.24(dd, 1H), 7.16(dd, 1H), 7.08(s, 1H), 7.06(s, 1H), 6.83 (dd, 1H), 4.34(m, 2H), 4.30(dd, 2H), 3.53 (dd, 2H), 3.32(m, 1H), 3.27 (q, 4H), 3.04(m, 2H), 1.99(m, 2H), 1.5 (Km, 2H), 1.28 (t, 6H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil] tiofen-3-carboxamida	77	389	1.22 (dd, 1H, J1=12.38Hz, J2=2.53Hz), 1.57(d, 1H, J=13.14Hz), 1.78(brt, 2H), 1.95 (brs, 1H), 2.60 (q, 1H, J=11.37), 2.78 (q, 1H, J=10.61 Hz), 3.09 (m, 1H), 3.25 (m, 3H), 3.77 (s, 3H), 6.97 (d, 2H, J=8.59 Hz), 7.44 (d, 2H, J=8.84 Hz), 7.58 (s, 1H), 8.24 (brs, 1H), 8.30 (brt, 1H), 8.57 (brs, 1H), 10.92 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1, 2,3,4-tetrahidroquinolin-3-il)tiofen-3-carboxamida	78	423		III
2-[(aminocarbonil)amino]-N-(1,3-benzodioxol-5-ilmetil)-5-(4-metoxifenil)tiofen-3-carboxamida	79	426	3.76 (s, 3H), 4.36 (d, 2H), 5.97 (s, 2H), 6.81 (d, 1H), 6.89 (d, 1H), 6.96 (d, 2H), 7.44 (d, 2H), 7.62 (s, 1H), 8.64 (t, 1H), 10.94 (s, 1H)	III
2-[(aminocarbonil)amino]-N-(3-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida	80	412	3.74 (s, 3H), 3.78 (s, 3H), 4.44 (d, 2H, J=5.56Hz), 6.82(m, 1H), 6.91(m, 2H), 6.98(d, 2H, J=8.59Hz), 7.25(t, 2H, J=7.83), 7.46(d, 2H,	III

			J=8.59Hz), 7.66(s, 1H), 8.71 (s, 1H, 10.95(s, 1H)	
2-[(aminocarbonil)amino]-N-[2-(3,4-dimetoxifenil) etil]-5-(4-metoxifenil)tiofen-3-carboxamida	81	456	3.73(s, 3H), 3.74(s, 3H), 3.77(s, 3H), 4.40(d, 2H, J=5.56Hz), 6.92(m, 7H), 7.45(d, 2H, J=8.34Hz), 7.66(s, 1H), 8.64(bs, 1H), 10.97(s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(5-metil-2-furil)metil]tiofen-3-carboxamida	84	386	2.22 (s, 3H), 3.76 (s, 3H), 4.38 (d, 2H), 5.99 (s, 1H), 6.14 (s, 1H), 6.96 (d, 2H), 7.43 (d, 2H), 7.64 (s, 1H), 8.57 (t, 1H), 10.93 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-2-ilmetil)tiofen-3-carboxamida	85	383	3.77 (s, 3H), 4.69 (d, 2H), 6.98 (d, 2H), 7.46 (d, 2H), 7.65 (t, 1H), 7.73(t, 1H), 7.67(s, 1H), 8.20 (t, 1H), 8.69 (d, 1H), 8.96 (t, 1H), 10.76 (s, 1H)	III
2-[(aminocarbonil)amino]-N-(4-fluorobencil)-5-(4-metoxifenil)tiofen-3-carboxamida	86	400		III
terc-butil 4-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil]carbonil}amino) piperidin-1-carboxilato	88	475		III
2-[(aminocarbonil)amino]-N-(2-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida	89	412	3.78(s, 3H), 3.83(s, 3H), 4.45(bd, 2h, J=5.56Hz), 6.97(m, 5H), 7.23(m, 2H), 7.47(d, 2H, J=8.84), 7.71 (s, 1H), 8.55(bt, 1H), 10.97(s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-fenoxietil)tiofen-3-carboxamida	90	412	3.56-3.7 (m, 2H), 3.76 (s, 3H), 4.11 (t, 2H), 6.85-7.05 (m, 5H), 7.28 (t, 2H), 7.44 (d, 2H), 7.61 (s, 1H), 8.38 (brs, 1H), 10.93 (s, 1H)	III
2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-2-iletil)tiofen-3-carboxamida	93	397	3.00 (t, 2H, J=7.45 Hz), 3.61 (m, 2H), 3.76 (s, 3H), 6.97 (d, 2H, J=8.84Hz), 7.22(dd, 1H, J1=6.95 Hz, J2=5.18 Hz), 7.27 (d, 1H, J=7.83 Hz), 7.43 (d, 2H, J=8.59 Hz), 7.54 (s, 1H), 7.70 (dt, 1H, J1=7.58 Hz, J2=1.77 Hz), 8.27(t, 1H, J=5.56Hz), 8.51 (d, 1H,	III

			J=4.55 Hz), 10.97 (s, 1H)	
terc-butil 4-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino) piperidin-1-carboxilato	94	475		III
2-[(aminocarbonil)amino]-N-(4-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida	95	412	3.72 (s, 3H), 3.76 (s, 3H), 4.39 (d, 2H), 6.89 (d, 2H), 6.96 (d, 2H), 7.25 (d, 2H), 7.44 (d, 2H), 7.63 (s, 1H), 8.64 (t, 1H), 10.95 (s, 1H)	III
2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida trifluoroacetato	110	460	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.60(dd, 2H), 3.50(m, 1H), 3.30(m, 5H), 2.95(dd, 2H), 2.10(dd, 2H), 1.80(m, 2H), 1.35(t, 6H)	IV
2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida trifluoroacetato	111	460	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.60(dd, 2H), 3.50(m, 1H), 3.30(m, 5H), 2.95(dd, 2H), 2.10(dd, 2H), 1.80(m, 2H), 1.35(t, 6H)	IV
terc-butil (3S)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi]fenil}-3-tienil)carbonil]amino} piperidin-1-carboxilato trifluoroacetato	112	560	MeOD; 7.55(d, 2H), 7.45(s, 1H), 7.05(d, 2H), 4.35(dd, 2H), 3.60-3.90(m, 3H), 3.60(dd, 2H), 3.30(m, 4H), 2.95(m, 2H), 1.90 (dd, 2H), 1.55(m, 2H), 1.45(s, 9H), 1.35(t, 6H)	IV
2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-{4-[2-(dietilamino)etoxi] fenil}tiofen-3-carboxamida clorhidrato	113	474	10.85(s, 1H), 9.50(brs, 1H), 9.10(br s, 1H), 8.95(brs, 1H), 8.20(d, 1H), 7.65(s, 1H), 7.50(d, 2H), 7.05(d, 2H), 6.95, (brs, 2H), 4.35(dd, 2H), 4.25(m, 1H), 3.50(dd, 2H), 3.10-3.40(m, 8H), 2.00(m, 1H), 1.80(m, 4H), 1.55(m, 1H), 1.25(t, 6H)	IV
terc-butil (3R)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi] fenil}-3-tienil)carbonil]amino} piperidin-1-carboxilato trifluoroacetato	114	560	MeOD; 7.45(d, 2H), 7.35(s, 1H) 6.90(d, 2H), 4.25(dd, 2H), 3.60-3.90(m, 3H), 3.50(dd, 2H), 3.20(m, 5H), 2.85(s, 1H), 1.80(dd, 2H), 1.45(m, 2H),	IV

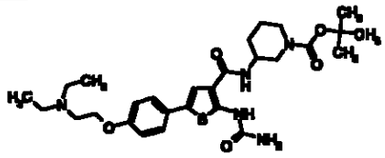
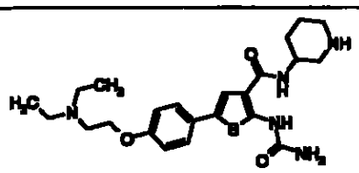
			1.35(s, 9H), 1.25(t, 6H)	
N-[3-{[(3S)-3-aminoazepan-1 -il] carbonil}-5-(4-metoxifenil)-2-tienil]urea clorhidrato	115	389	9.65 (s, 1H), 8.25 (s, 3H), 7.50 (d, 2H), 7.10(s, 1H), 6.90(d, 2H), 6.75 (br s, 2H), 4.00 (m, 1H), 3.80(s, 3H), 3.40 (m, 4H), 2.0 (m, 1H), 1.00-1.80 (m, 5H)	IV
2-({[(2, 5-dimetoxifenil)amino] carbonil}amino)-5-(4-metoxifenil)-N-piperidin-3-iltiofen-3-carboxamida	116	511	11.28 s 1H, 9.65 bs 1H, 9.08 bs 1H, 8.43 s 1H, 7.90 s 1H, 7.46 d J = 8.7 Hz 2H, 6.83 d J = 8.8 Hz 2H, 6.65 d J = 8.8 Hz 1H, 6.43 - 6.47 m 1H, 4.35 bs 1H, 3.76 s 3H, 7.73 s 3H, 3.54 s 3H, 3.24-3.45 m 2H, 2.81 bs 2H, 2.44 bs 4H.	V
5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida	120	524	1.21 (t, 6H), 2.00 (m, 1H), 2.20 (m, 1H), 3.18 (m, 4H), 3.43 (m, 6H), 4.31 (t, 2H), 4.53 (m, 1H), 7.05 (d, 2H), 7.52 (d, 2H), 7.70 (s, 1H), 8.30 (m, 3H), 8.78 (s, 1H), 8.85 (s, 1H), 8.98 (s, 1H), 9.32 (s, 1H) 10.90 (s, 1H)	VI
5-{3-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida clorhidrato	121	524	1.25 (t, 6H), 2.02 (m, 1H), 2.20 (m, 1H), 3.22 (m, 4H), 3.43 (m, 6H), 4.34 (t, 2H), 4.53 (m, 1H), 6.92 (d, 1H), 7.12 (s, 1H), 7.28 (d, 1H), 7.39 (dxd, 1H), 7.84 (s, 1H), 8.32 (m, 3H), 8.78 (s, 1H), 8.85 (s, 1H), 8.98 (s, 1H), 9.30 (s, 1H), 10.92 (s, 1H)	VI
5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida	122	538	): 0.95 (t, 6H), 1.52 (m, 2H), 1.62 (m, 4H), 2.52 (m, 4H), 2.78 (m, 4H), 3.00 (m, 12H), 3.18 (t, 2H), 4.05 (t, 2H), 6.68 (bs, 1H), 6.80 (d, 1H), 7.10 (m, 2H), 7.28 (m, 2H), 7.82 (s, 1H), 8.22 (s, 1H), 8.28 (s, 1H), 9.00 (s, 1H)	VI
N-[(3S)-azepan-3-il]-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida clorhidrato	123	467	δ 12.6, brs, 1H; δ 10.9, s, 1H; δ 9.55, brs, 1H; δ 9.24, brs, 1H; δ 8.88, s, 1H; δ 8.49, d, 1H; δ 8.35, dd, 1H; δ 8.29, d, 1H; δ 7.92, s, 1H; δ	VI

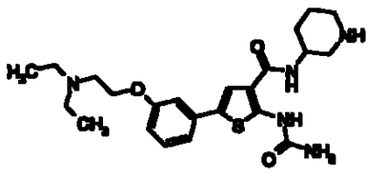
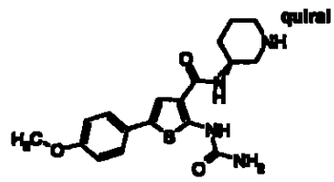
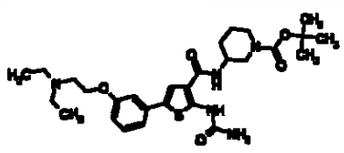
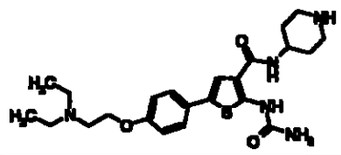
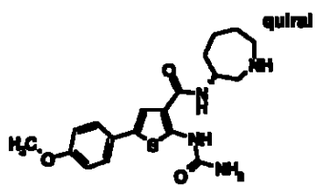
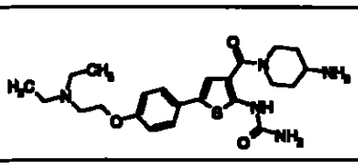
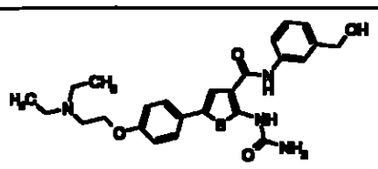
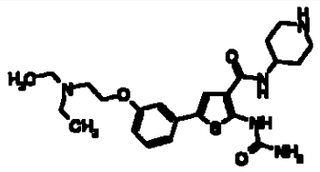
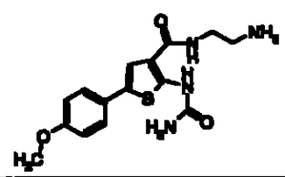
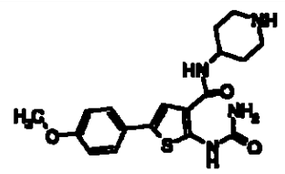
			7.54, d, 2H; δ 6.99, d, 2H; δ 4.42, m, 1H; δ 3.33, m, 1H; δ 3.23, m, 2H; δ 3.10, m, 1H; δ 2.02, m, 1H; δ 1.85, m, 4H; δ 1.62, m, 1H	
5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida clorhidrato	124	538	0.95 (t, 6H), 1.52 (m, 2H), 1.62 (m, 4H), 2.52 (m, 4H), 2.78 (m, 4H), 3.00 (m, 12H), 3.18 (t, 2H), 4.05 (t, 2H), 6.68 (bs, 1H), 6.80 (d, 1H), 7.10 (m, 2H), 7.28 (m, 2H), 7.82 (s, 1H), 8.22 (s, 1H), 8.28 (s, 1H), 9.00 (s, 1H)	VI
N-(2-aminoetil)-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida	125	413	8.53 s 1H, 8.31-8.33 m 1H, 8.13 d J=2.8 Hz 1H, 7.42 d J=8.8 Hz 2H, 7.38 s 1H, 6.85 d J=8.8 Hz 2H, 3.72 s 3H.	VI
5-{4-[2-(dietilamino) etoxi]fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino)carbonil] amino} tiofen-3-carboxamida	126	538	0.95 (t, 6H), 1.52 (m, 2H), 1.79 (m, 2H), 2.42 (m, 4H), 2.70 (m, 4H), 3.08 (m, 2H), 3.98 (m, 3H) 6.95 (d, 2H), 7.48 (d, 2H), 7.70 (s, 1H), 8.28 (d, 2H), 8.95 (s, 1H)	VI
5-(4-metoxifenil)-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida	127	453		VI
terc-butil 3-{[(5-{3-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-3-tienil)carbonil]amino} piperidin-1-carboxilato trifluoroacetato	128	638	1.21 (t, 6H), 1.32 (s, 9H), 1.75 (m, 1H), 1.92 (m, 1H), 2.85 (m, 1H), 3.20 (m, 4H), 3.50 (t, 2H), 3.80 (m, 2H), 4.35(t, 2H), 6.90 (d, 1H), 7.15 (s, 1H) 7.25 (d, 1H), 7.38 (dxd, 1H), 7.76 (s, 1H), 7.98 (bs, 1H), 8.30 (d, 2H), 8.90 (s, 1H), 9.25 (bs, 1H), 10.92(s, 1H)	VI
5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida	129	538	0.95 (t, 6H), 1.52 (m, 2H), 1.79 (m, 2H), 2.42 (m, 4H), 2.70 (m, 4H), 3.08 (m, 2H), 3.98 (m, 3H), 6.95 (d, 2H), 7.48 (d, 2H), 7.70 (s, 1H), 8.28 (d, 2H), 8.95 (s, 1H)	VI
5-(4-metoxifenil)-2-	130	439		VI

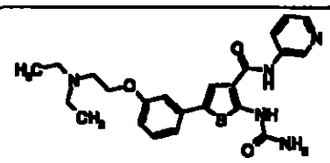
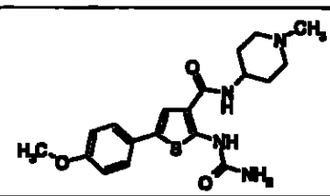
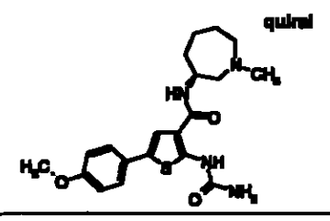
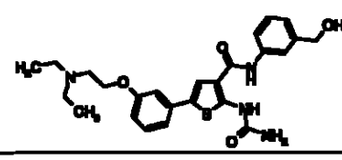
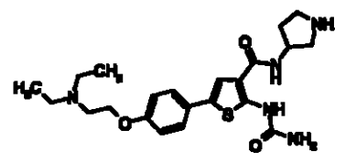
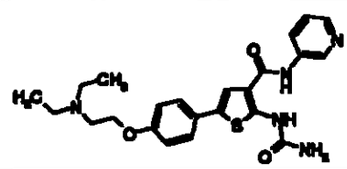
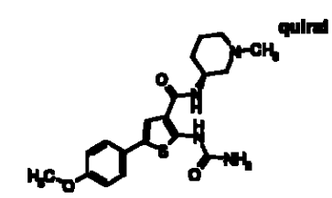
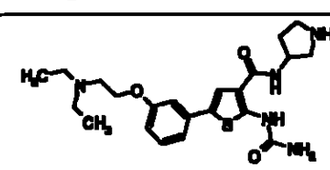
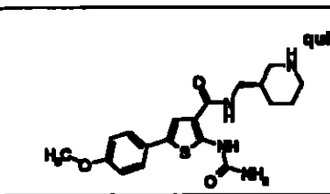
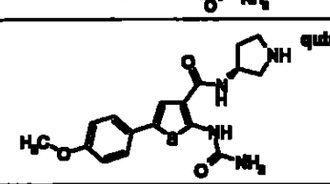
{[(pirazin-2-ilamino) carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida				
N-[3-(1,4-diazepan-1 -ilcarbonil)-5-{4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea	131	453	8.47 s 1H, 8.14-8.25 m 2H, 7.43 d J=8.8 Hz 2H, 7.06 s 1H, 7.85 d J=8.8 Hz 2H, 3.90 bs 2H, 3.79 t J=6.0 Hz 2H, 3.72 s 3H, 3.40 bs 2H, 2.10 bs 2H.	VI
N-[3-[(3-aminopirrolidin-1 -il)carbonil]-5-(4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea	132	439	11.97 bs 1H, 10.72 s 1H, 8.79 s 1H, 8.22-8.26 m 2H, 7.50 d J=8.6 Hz 2H, 8.04 bs 2H, 7.31 s 1H, 7.20-7.25 m 2H, 7.08 d J=8.3 Hz 1H, 7.00 t J=7.2 Hz 1H, 6.92 d J=8.6 Hz 2H3.72 s 3H, 2.11-2.19 m 1H, 3.80 bs 2H, 3.64 bs 2H.	VI
terc-butil 4-{[(5-(4-metoxifenil)-2-{[(pirazin-2-ilamino) carbonil]amino}-3-tienil)carbonil]amino} piperidin-1-carboxilato	133	553		VI
terc-butil 3-{[(5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-3-tienil)carbonil]amino} piperidin-1-carboxilato	134	638	1.18 (t, 6H), 1.32 (s, 9H), 1.72 (m, 1H), 1.90 (m, 1H), 2.85 (m, 1H), 3.21 (m, 4H), 3.50 (t, 2H), 3.80 (m, 2H), 4.30 (t, 2H), 7.05 (d, 2H), 7.52 (d, 2H), 7.76 (s, 1H), 7.92 (bs, 1H), 8.30 (d, 2H) 8.90 (s, 1H), 9.25 (bs, 1H), 10.90(s, 1H)	VI
5-[4-(2-dietilamino-etoxi)-fenil]-2-(3-hidroxi-urea)-tiofen-3-ácido carboxílico - (S)-piperidin-3-ilamida	136	476	δ 1.17 -1.40 (m, 6H) 1.54 -1.81 (m, 2H) 1.84-2.07 (m, 2H) 2.76 - 2.99 (m, 2H) 3.05-3.25 (m, 4H) 3.41 - 3.61 (m, 4H) 3.73 - 3.88 (m, 1H) 4.29 -4.42 (m, 1H) 4.40 - 4.64 (m, 1 H) 5.86 (s, 1H) 7.07 (d, *J*=8.48 Hz, 2H) 7.55 (d, *J*=8.48 Hz, 2 H) 7.82 (s, 1H) 9.44 (s, 1H) 9.65 (s, 1H);	VII
2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(3-metoxifenil)tiofen-3-carboxamida	137	389	10.90 (s, 1H), 9.21 (s, 1H), 9.01 (s, 1H), 8.29 (d, 1H), 7.93 (s, 1H), 7.29 (t, 1H), 7.11 (d, 2H), 7.03 (s, 1H), 6.83 (d, 1H), 4.33 (s, 1H),	VIII

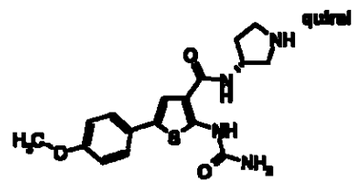
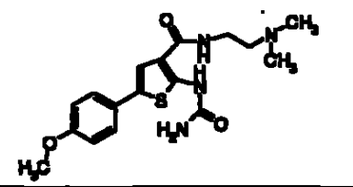
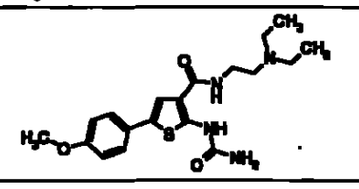
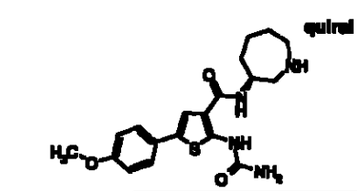
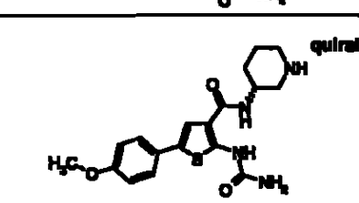
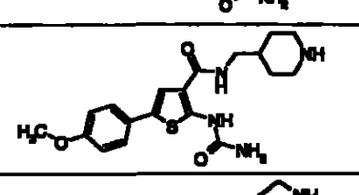
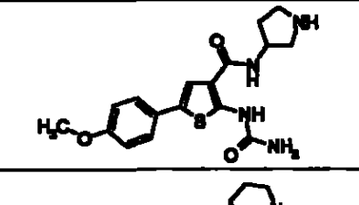
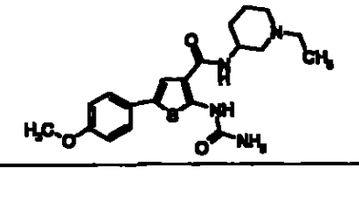
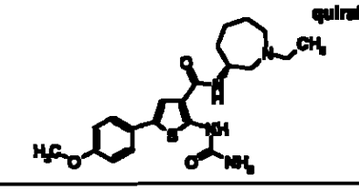
			3.81 (s, 3H), 3.20 (m, 4H), 2.00 (m, 1H), 1.84 (m, 4H), 1.56 (m, 1H).	
2-[(aminocarbonil)amino]-5-(2-hidroxifenil)-*N*-[(3*S*)-piperidin-3-il]tiofen-3-carboxamida	138	361	δ 10.85 (s, 1H), 10.13 (s, 1H), 9.29 (d, 2H), 8.31 (d, 1H), 7.92 (s, 1H), 7.63 (dd, 1H), 7.05 (td, 1H), 6.94 (dd, 1H), 6.82 (td, 1H), 6.91 (brs, 2H), 4.21 (brs, 1H), 3.26 (dd, 2H), 2.89 (m, 2H), 1.88-1.618 (m, 4H).	VIII
2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-[(3S)-piperidin-3-il] tiofen-3-carboxamida	139	375	10.94 (s, 1H), 9.41 (s, 1H), 9.19 (s, 1H), 8.47 (d, 1H), 8.11 (s, 1H), 7.30 (t, 1H), 7.15(d, 1H), 7.05 (br, 2H), 6.84 (d, 1H), 4.25 (s, 1H), 3.82 (s, 3H), 3.29 (d, 1H), 3.12 (d, 1H), 2.97 (m, 2H), 1.92 (d, 2H), 1.69 (m, 2H).	VIII
2-[(aminocarbonil)amino]-5-[2-(benciloxi)fenil]-*N*-[(3*S*)-piperidin-3-il]tiofen-3-carboxamida	140	451	δ 10.8 (s, 1H), 8.63 (brs, 2H), 8.04 (d, 1H), 7.79 (s, 1H), 7.63 (d, 1H), 7.55 (d, 2H), 7.38 (t, 2H), 7.31 (t, 1H), 7.23 (t, 1H), 7.20 (t, 1H), 7.02 (t, 1H), 6.95 (m, 2H), 5.28 (s, 2H), 4.15 (m, 1H), 3.24 (m, 1H), 2.85 (m, 2H), 1.90-1.58 (m, 5H).	VIII

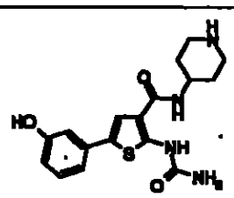
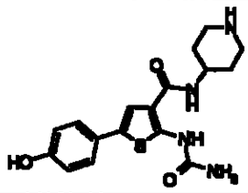
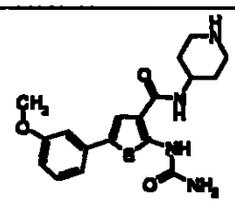
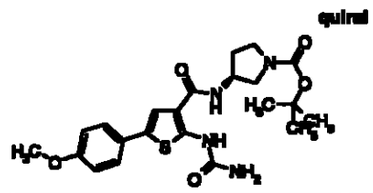
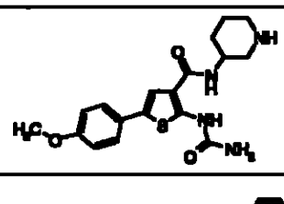
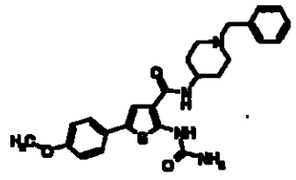
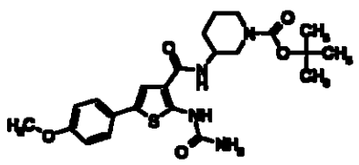
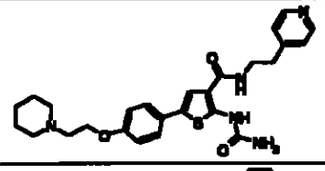
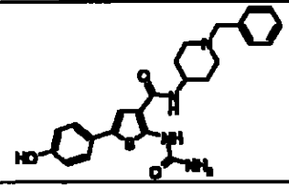
Tabla 2

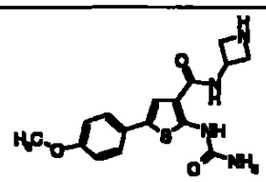
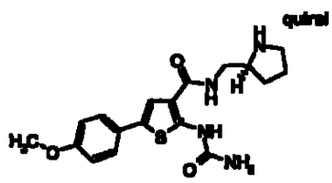
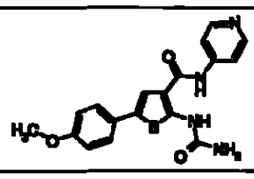
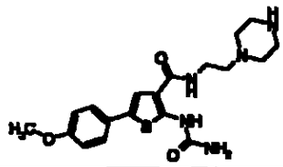
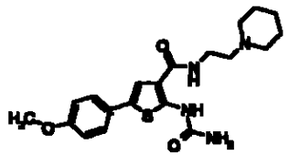
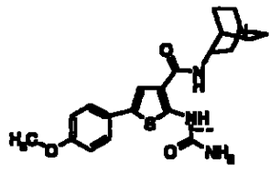
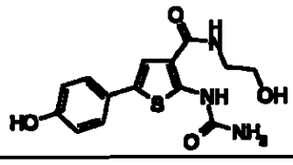
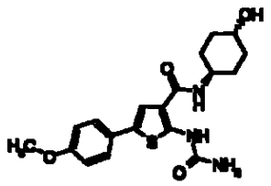
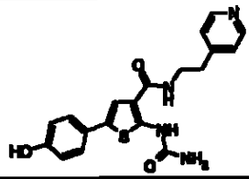
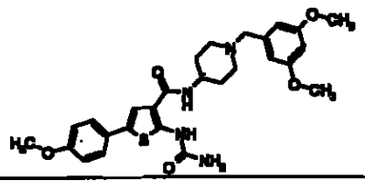
Estructura	Designación de la IUPAC	M.W. (g/mol)	Ej.
	*terc*-butil3-{[(2-[(aminocarbonil) amino]-5-{4-[2-(dietilamino) etoxi]fenil}-3-tienil)carbonil] amino}piperidin-1-carboxilato trifluoroacetato	559.7	1
	2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida trifluoroacetato	459.6	2

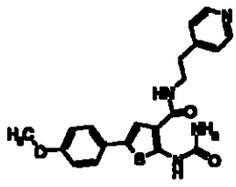
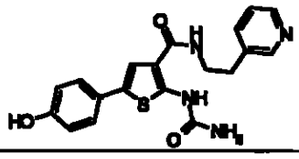
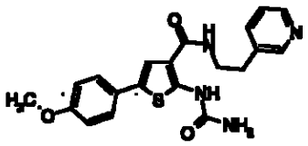
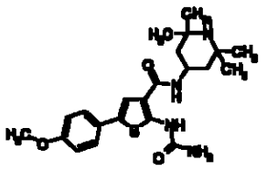
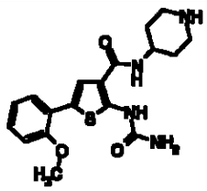
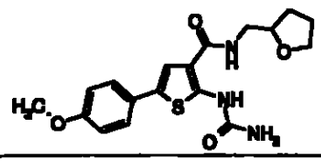
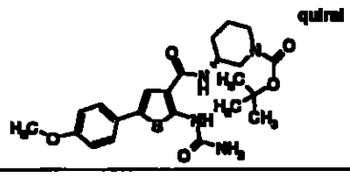
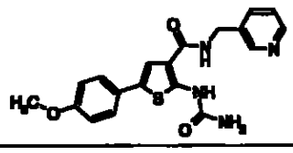
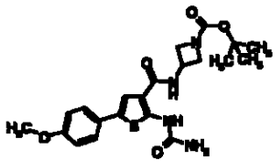
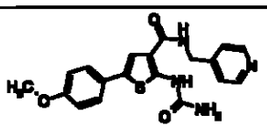
	2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida trifluoroacetato	459.6	3
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida	374.5	4
	*terc*-butil 3-{[(2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato trifluoroacetato	559.7	5
	2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida	549.6	6
	2-[(aminocarbonil)amino]-N-[(3R)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida	388.5	7
	N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{4-[2-(dietilamino)etoxi]fenil}-2-tienil)urea trifluoroacetato	459.6	8
	2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida trifluoroacetato (sal)	482.6	9
	2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida trifluoroacetato	459.6	10
	2-[(aminocarbonil)amino]-N-(2-aminoetil)-5-(4-metoxifenil)tiofen-3-carboxamida	334.4	11
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida	374.5	12

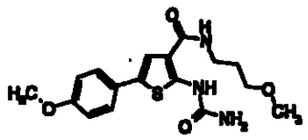
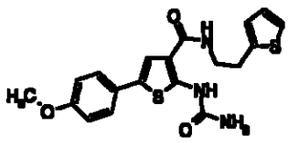
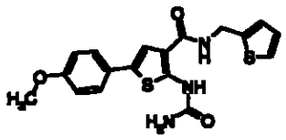
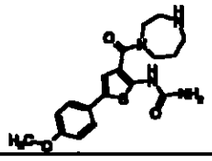
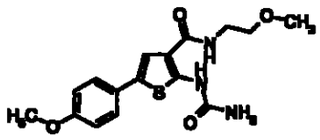
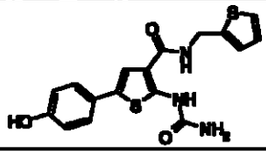
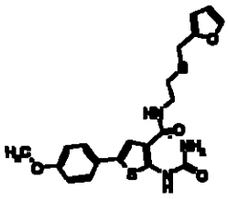
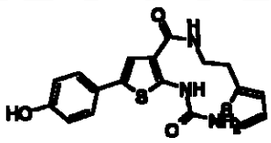
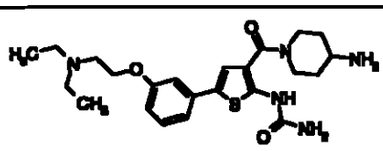
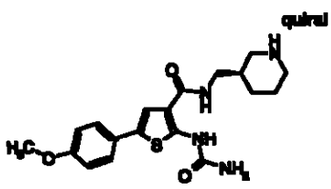
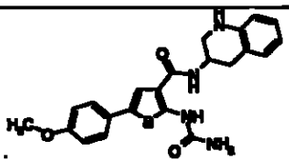
	2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida trifluoroacetato	453.6	13
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1-metilpiperidin-4-il)tiofen-3-carboxamida	388.5	14
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilazepan-3-il]tiofen-3-carboxamidaclorhidrato	402.5	15
	2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida trifluoroacetato (sal)	482.6	16
	2-[(aminocarbonil)amino]-5-{4- [2-(dietilamino)etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida trifluoroacetato	445.6	17
	2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida trifluoroacetato	453.6	18
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilpiperidin-3-il]tiofen-3-carboxamida clorhidrato	388.5	19
	2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida trifluoroacetato	445.6	20
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil]tiofen-3-carboxamida	388.5	21
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida	360.4	22

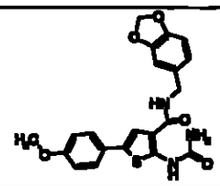
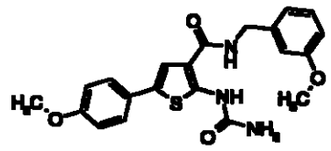
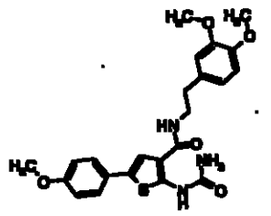
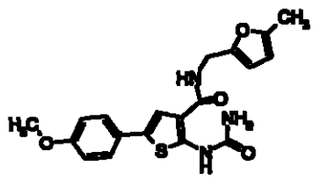
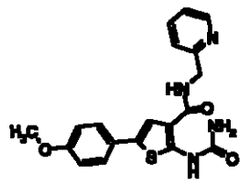
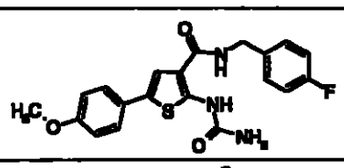
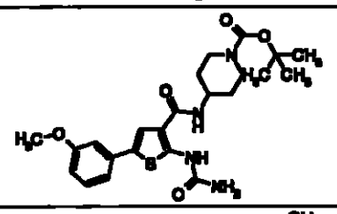
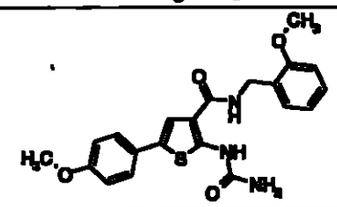
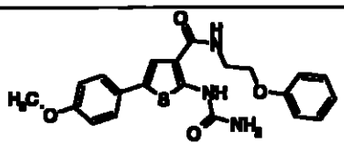
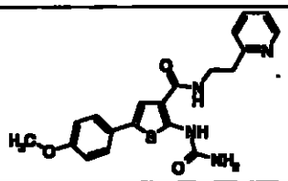
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-pirrolidin-3-il]tiofen-3-carboxamida	360.4	23
	2-[(aminocarbonil)amino]-N-[2-(dimetilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida	362.4	24
	2-[(aminocarbonil)amino]-N-[2-(dietilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida	390.5	25
	2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato	388.5	26
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida	374.5	27
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piperidin-4-ilmetil)tiofen-3-carboxamida	388.5	28
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-pirrolidin-3-iltiofen-3-carboxamida	360.4	29
	2-[(aminocarbonil)amino]-N-(1-etilpiperidin-3-il)-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato	402.5	30
	2-[(aminocarbonil)amino]-N-[(3S)-1-etilazepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato	416.5	31

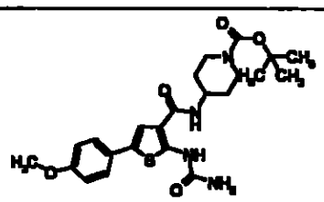
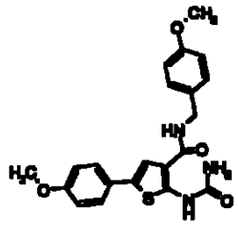
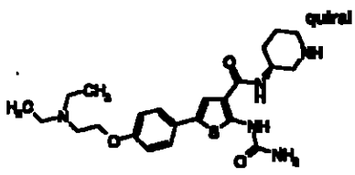
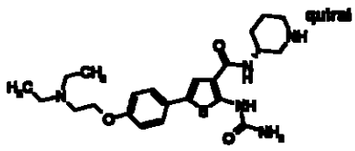
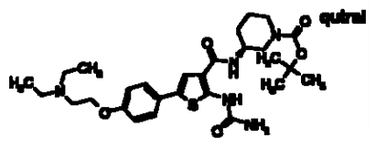
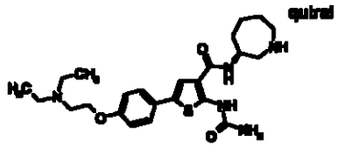
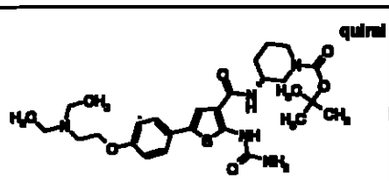
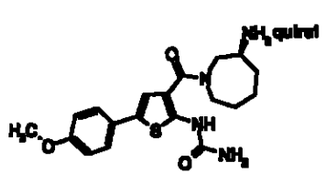
	2-[(aminocarbonil)amino]-5-(3-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida	360.4	32
	2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida	360.4	33
	2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida	374.5	34
	*terc*-butil (3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)pirrolidin-1-carboxilato	460.6	35
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-3-iltiofen-3-carboxamida	374.5	36
	2-[(aminocarbonil)amino]-N-(1-bencilpiperidin-4-il)-5-(4-metoxifenil)tiofen-3-carboxamida	464.6	37
	*terc*-butil 3-({[2-[(aminocarbonil) amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino)piperidin-1-carboxilato	474.6	38
	2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida	493.6	39
	2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida	450.6	40

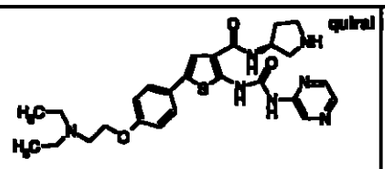
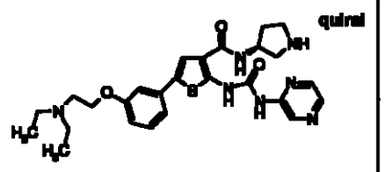
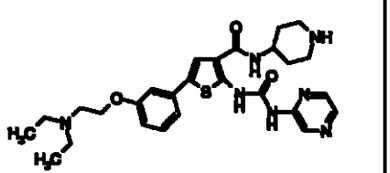
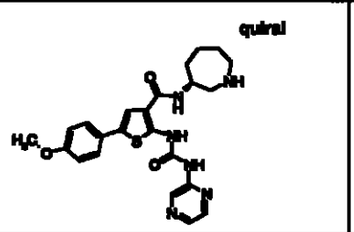
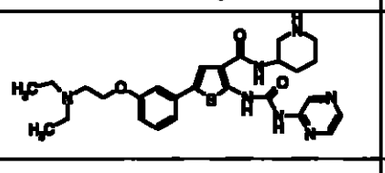
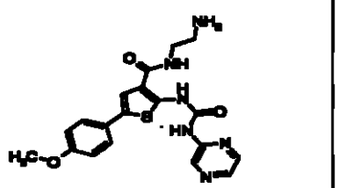
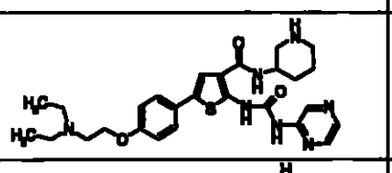
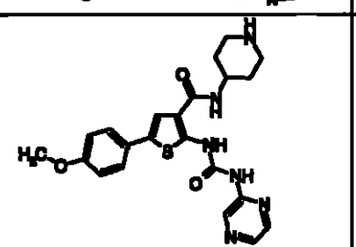
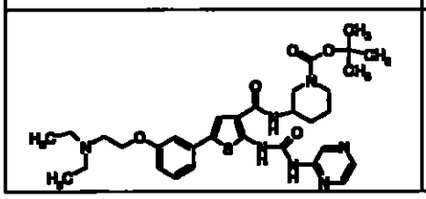
	2-[(aminocarbonil)amino]-N-azetidin-3-il-5-(4-metoxifenil)tiofen-3-carboxamida	346.4	41
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(2S)-pirrolidin-2-ilmetil]tiofen-3-carboxamida	374.5	42
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piridin-4-iltiofen-3-carboxamida	368.4	43
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida	403.5	44
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperidin-1-iletil)tiofen-3-carboxamida	402.5	45
	2-[(aminocarbonil)amino]-N-1-azabiciclo[2.2.2]oct-3-il-5-(4-metoxifenil)tiofen-3-carboxamida	400.5	46
	2-[(aminocarbonil)amino]-N-(2-hidroxietil)-5-(4-hidroxifenil)tiofen-3-carboxamida	321.4	48
	2-[(aminocarbonil)amino]-N-(trans-4-hidroxiciclohexil)-5-(4-metoxifenil)tiofen-3-carboxamida	389.5	49
	2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida	382.4	50
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida	524.6	52

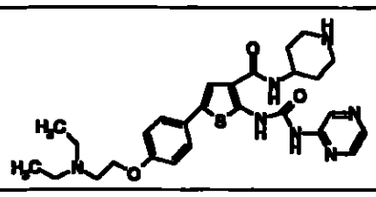
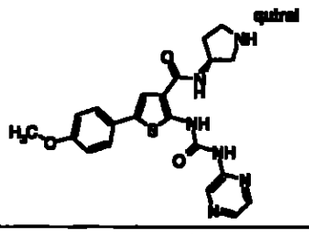
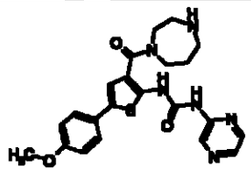
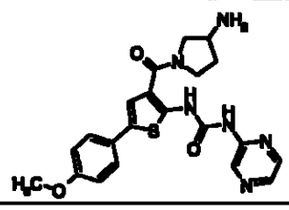
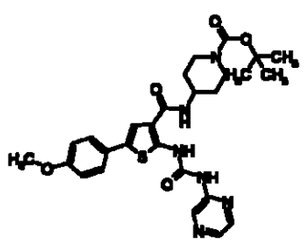
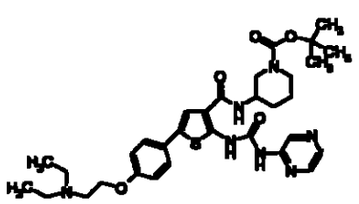
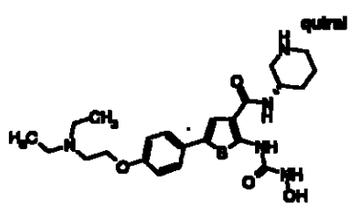
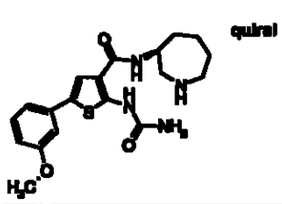
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida	396.5	54
	2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida	382.4	55
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida	396.5	56
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2,2,6,6-tetrametilpiperidin-4-il)tiofen-3-carboxamida	430.6	58
	2-[(aminocarbonil)amino]-5-(2-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida	374.5	59
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(tetrahidrofuran-2-ilmetil)tiofen-3-carboxamida	375.4	60
	*terc*-butil (3R)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino)piperidin-1-carboxilato	474.6	62
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-3-ilmetil)tiofen-3-carboxamida	382.4	63
	*terc*-butil 3-({[2-[(aminocarbonil) amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino)azetidin-1-carboxilato	446.5	64
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-4-ilmetil)tiofen-3-carboxamida	382.4	65

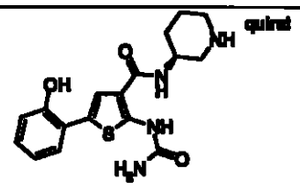
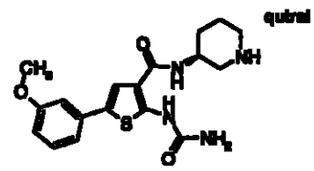
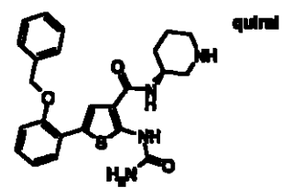
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(3-metoxipropil)tiofen-3-carboxamida	363.4	67
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida	401.5	68
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida	387.5	69
	N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]urea	374.5	70
	2-[(aminocarbonil)amino]-N-(2-metoxietil)-5-(4-metoxifenil)tiofen-3-carboxamida	349.4	71
	2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida	373.5	72
	2-[(aminocarbonil)amino]-N-{2-[(2-furilmetil)tio]etil}-5-(4-metoxifenil)tiofen-3-carboxamida	431.5	74
	2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-[2-(2-tienil) etil]tiofen-3-carboxamida	387.5	75
	N-(3-[(4-aminopiperidin-1-il) carbonil}-5-{3-[2-(dietilamino)etoxi]fenil}-2-tienil)urea trifluoroacetato	459.6	76
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil]tiofen-3-carboxamida	388.5	77
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1,2,3,4-tetrahidroquinolin-3-il)tiofen-3-carboxamida	422.5	78

	2-[(aminocarbonil)amino]-N-(1,3-benzodioxol-5-ilmetil)-5-(4-metoxifenil)tiofen-3-carboxamida	425.5	79
	2-[(aminocarbonil)amino]-N-(3-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida	411.5	80
	2-[(aminocarbonil)amino]-N-[2-(3,4-dimetoxifenil)etil]-5-(4-metoxifenil)tiofen-3-carboxamida	455.5	81
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(5-metil-2-furil)metil]tiofen-3-carboxamida	385.4	84
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-2-ilmetil)tiofen-3-carboxamida	382.4	85
	2-[(aminocarbonil)amino]-N-(4-fluorobencil)-5-(4-metoxifenil)tiofen-3-carboxamida	399.4	86
	*terc*-butil 4-({[2-[(aminocarbonil) amino]-5-(3-metoxifenil)-3-tienil]carbonil}amino)piperidin-1-carboxilato	474.6	88
	2-[(aminocarbonil)amino]-N-(2-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida	411.5	89
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-fenoxietil)tiofen-3-carboxamida	411.5	90
	2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-2-iletil)tiofen-3-carboxamida	396.5	93

	*terc*-butil 4-({[2-[(aminocarbonil) amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino)piperidin-1-carboxilato	474.6	94
	2-[(aminocarbonil)amino]-N-(4-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida	411.5	95
	2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida trifluoroacetato	459.6	110
	2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida trifluoroacetato	459.6	111
	*terc*-butil (3S)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato trifluoroacetato	559.7	112
	2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-(dietilamino)etoxi] fenil}tiofen-3-carboxamida clorhidrato	473.6	113
	*terc*-butil (3R)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato trifluoroacetato	559.7	114
	N-[3-{[(3S)-3-aminoazepan-1-il]carbonil}-5-(4-metoxifenil)-2-tienil]urea clorhidrato	388.5	115

	5-{4-[2-(dietilamino)etoxi] fenil}-2-{[(pirazin-2-ilamino) carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida	523.7	120
	5-{3-[2-(dietilamino)etoxi] fenil}-2-{[(pirazin-2-ilamino) carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida clorhidrato	523.7	121
	5-{3-[2-(dietilamino)etoxi] fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida	537.7	122
	N-[(3S)-azepan-3-il]-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino}tiofen-3-carboxamida clorhidrato	466.6	123
	5-{3-[2-(dietilamino)etoxi] fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida clorhidrato	537.7	124
	N-(2-aminoetil)-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino}tiofen-3-carboxamida	412.5	125
	5-{4-[2-(dietilamino)etoxi] fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida	537.7	126
	5-(4-metoxifenil)-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida	452.5	127
	*terc*-butil 3-{[(5-{3-[2-dietilamino) etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato trifluoroacetato	637.8	128

	5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil]amino}tiofen-3-carboxamida	537.7	129
	5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida	438.5	130
	N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]-N'-pirazol-2-ilurea	452.5	131
	N-[3-[(3-aminopirrolidin-1-il)carbonil]-5-(4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea	438.5	132
	*terc*-butil 4-{[(5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}-3-tienil)carbonil]amino} piperidin-1-carboxilato	552.6	133
	*terc*-butil 3-{[(5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil] amino}-3-tienil)carbonil]amino} piperidin-1-carboxilato	637.8	134
	5-[4-(2-dietilamino-etoxi)-fenil]-2-(3-hidroxi-urea)-tiofen-3-ácido carboxílico -(S)-piperidin-3-ilamida	475.2	136
	2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(3-metoxifenil)tiofen-3-carboxamida	388.5	137

	2-[(aminocarbonil)amino]-5-(2-hidroxifenil)-*N*-[(3*S*)-piperidin-3-il]tiofen-3-carboxamida	360.4	138
	2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida	374.5	139
	2-[(aminocarbonil)amino]-5-[2-(benciloxi)fenil]-*N*-[(3*S*)-piperidin-3-il]tiofen-3-carboxamida	450.6	140

Ejemplo 4

2-[(Aminocarbonil)aminol-5-(4-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida

(4-Metoxi-fenil)-acetaldehído. A una solución agitada de éster metílico de ácido (4-metoxi-fenil)-acético (18.0 g, 100 mmol) en tolueno anhidro (200mL) enfriado a -78°C bajo N_2 se agregó hidruro de diisobutilaluminio (DIBAL, 1.0 M en tolueno, 150 mL, 150 mmol) durante un período de 10-15 minutos. La mezcla se agitó a -78°C durante 2 horas adicionales. La reacción se extinguió por la lenta adición de MeOH, seguida por la introducción de 10% de sal de Rochelle. La suspensión se diluyó con EtOAc y se agitó a temperatura de la sala durante 1 hora. La capa EtOAc se reservó y la capa acuosa se extrajo con EtOAc (2x). Las capas orgánicas se combinaron y se secaron sobre Na_2SO_4 y se filtraron. La solución se concentró bajo vacío para producir 12.0 g (100%) del aldehído del título como un semisólido viscoso amarillo, el cual se utilizó en el siguiente paso sin purificación. LC/MS (APCI, ES, M+H=151).

Éster metílico de ácido 2-amino-5-(4-metoxi-fenil)-tiofen-3-carboxílico. A una solución de 4-metoxifenilacetaldehído (12.0g) en DMF (200mL) se

agregó acetato de cianometilo (8.9 mL, 100 mmol) y azufre (3.2g, 100mmol), seguido por diisopropiletilamina (base de Hünig, 17.4 mL, 100 mmol). Inmediatamente la suspensión resultante se volvió amarillo oscuro a marrón con una exoterma. La mezcla de reacción se agitó de un día para otro a temperatura de la sala. La reacción se agregó lentamente a agua (~1L) agitando al mismo tiempo. Se formó un precipitado de color café claro y se filtró después de 30 minutos adicionales de agitación. El sólido resultante se purificó por cromatografía de columna (SiO_2, 10-20% EtOAc/hexanos) para producir 15.3 g (58%) del compuesto del título como un sólido amarillo claro. ^{1}H NMR (d_6-DMSO δ 7.41, br s, 2H; δ 7.37, d, 2H; δ 7.07, s, 1H; δ 6.90, d, 2H; δ 3.75, s, 3H; δ 3.72, s, 3H), LC/MS (APCI, ES, M+H=264).

Metil 5-(4-metoxifenil)-2-({[(tricloroacetil)amino]carbonil}amino) tiofen-3-carboxilato. A una solución agitada de éster metílico de ácido 2-amino-5-(4-metoxi-fenil)-tiofen-3-carboxílico (7.15 g, 27.2 mmol) en THF anhidro (150 mL) se agregó tricloroacetil isocianato (6.4mL, 54 mmol) lentamente durante un período de 5 minutos. Una vez completa la adición, se formó un precipitado y la reacción se agitó durante 1 hora más. El producto deseado se obtuvo por filtración para producir 6.9 g (56%) de un sólido blancuzco. El producto se utilizó en el siguiente paso sin purificación. ^{1}H NMR (d_6-DMSO δ 12.3, br s, 1H; δ 12.2, s, 1H; δ 7.46, d, 2H; δ 7.32, s, 1H; δ 6.85, d, 2H; δ 3.75, s, 3H; δ 3.66, s, 3H), LC/MS (APCI, ES, M+H=451).

***terc*-Butil (3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato.** A una solución de metil 5-(4-metoxifenil)-2-({[(tricloroacetil)amino]carbonil}amino)tiofen-3-carboxilato (1.0 g, 2.2 mmol) en THF seco (20 mL) se agregó una solución de [Me_2Al-3-Boc-(S)-3-aminopiperidina] en THF (que se preformó por la adición de Me_3Al (2.0 M en hexanos, 2.2 mL, 4.4 mmol) a una solución de *terc*-butil éster de ácido (S)-3-amino-piperidin-1-carboxílico (0.89 g, 4.4 mmol) en

10 mL THF a -78°C seguido por calentamiento a temperatura de la sala durante 15 minutos más). La solución de color naranja resultante se agitó de un día para otro a temperatura de la sala. La mezcla de reacción se enfrió con hielo y se agregó lentamente 10% de una solución acuosa de sal de Rochelle para extinguir la reacción. La solución bifásica resultante se calentó a temperatura de la sala y se agitó durante 1 hora más. La mezcla se diluyó con EtOAc y M_2O, la capa acuosa se extrajo con EtOAc (3x) y los extractos orgánicos combinados se lavaron con M_2O, salmuera y se secaron (Na_2SO_4). La evaporación produjo un sólido anaranjado pálido. La purificación por cromatografía de columna (SiO_2, 50 % EtOAc/hexanos) produjo 0.70 g (67%) de un sólido amarillo claro. LC/MS (APCl, ES, M+H=475).

2-[(Aminocarbonil)amino]-5-(4-metoxifenil)-*N*-[(3*S*)-piperidin-3-il] tiofen-3-carboxamida; clorhidrato. A una solución agitada de *terc*-butil (3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato (0.70 g, 1.47 mmol) en MeOH anhidro (5.0 mL) se agregó 4.0N HCl en 1,4-dioxano (10 mL). Poco después se forma una pequeña cantidad de precipitado y la reacción se agita durante 4 horas más a temperatura de la sala. El disolvente se retiró bajo vacío. El residuo se redisolvió en metanol y se concentró bajo vacío (2x) para producir 0.51 g (85%) de un sólido amarillo claro. ^{1}H NMR (d_6-DMSO δ 10.9, s, 1H; δ 9.39, br s, 1H; δ 9.20, br s, 1H; δ 8.37, d, 1H; δ 7.88, s, 1H; δ 7.49, d, 2H; δ 6.96, d, 2H; δ 6.97, br s, 2H; δ 4.24, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.11, m, 1H; δ 2.93, m, 2H; δ 1.91, m, 2H; δ 1.68, m, 2H), LC/MS (APCI, ES, M+H=6875).

Ejemplo 26

2-[(Aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida clorhidrato

***terc*-Butil éster de ácido (S)-3-amino-azepan-1-carboxílico.** (S)-Azepan-3-ilamina (5g; 43.8 mmol) se disolvió en 100 mL de CH_2Cl_2 (diclorometano) anhidro y se enfrió a -78°C agitando al mismo tiempo con una barra de agitación magnética. En otro matraz se disolvió N-(*terc*-butoxicarboniloxi)succinimida [Boc-OSu] (9.7 g 45 mmol) en 50 mL de CH_2Cl_2 anhidro. A la solución agitada de la amina se agregó la solución de la succinimida durante un período de 10-15 minutos, con el fin de mantener la mezcla de reacción a -78 °C agitando simultáneamente. Una vez completa la adición, la reacción se dejó calentar a temperatura de la sala y se agitó durante 4 horas más o hasta que la reacción se completó por TLC (Ninhidrina; R_f 0.3; 0.1:1:10 NH_4OH, MeOH; CH_2Cl_2). La mezcla de reacción se lavó con 50 mL de H_2O. La capa acuosa se llevó a un pH >13 mediante la adición de 6N NaOH y se extrajo con CH_2Cl_2 (3 x 100 mL). La capa orgánica se secó sobre Na_2CO_3, se filtró y se concentró en vacío para producir *terc*-butil éster de ácido (S)-3-amino-azepan-1-carboxílico puro como un aceite viscoso (5.1 g, 54%). ^{1}H NMR (d_6-DMSO, d 3.4, m, 2H; d 2.89, m, 1H; d 2.71, m, 1H; d 2.54, m, 1H; d 1.54, m, 3H; d 1.34, m, 3H; d 1.27, s, 9H; d 1.12, m, 2H), LC/MS (APCI, ES, M+H=215).

***terc*-Butil (3*S*)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)azepan-1-carboxilato.** A una solución de metil 5-(4-metoxifenil)-2-({[(tricloroacetil)amino]carbonil}amino)tiofen-3-carboxilato (1.36 g, 3 mmol) en THF anhidro (20 mL) se agregó una solución de [Me_2Al-3-Boc-(S)-3-aminohomopiperidina] en THF (preformado por la cuidadosa adición de Me_3Al (2.0 M en hexanos, 3.0 mL, 6.0 mmol) a una solución de *terc*-butil éster de ácido (S)-3-amino-azepan-1-carboxílico en 10 mL de THF a -78°C seguido por calentamiento a temperatura de la sala bajo nitrógeno y agitando durante 15 minutos más. La solución resultante de color anaranjado/amarillo profundo se agitó de un día para otro a temperatura de la sala. La mezcla de reacción se enfrió con hielo y se agregó 10% de una solución acuosa de sal de Rochelle lentamente para extinguir la reacción. La solución bifásica resultante se calentó a

temperatura de la sala y se agitó durante 1 hora más. La mezcla se diluyó con EtOAc y tiroides H_2O, la capa acuosa se extrajo con EtOAc (3x) y los extractos orgánicos combinados se lavaron con H_2O, salmuera y se secaron (Na_2SO_4). La evaporación produjo un sólido amarillo pálido. La purificación por ISCO MPLC (SiO_2, 60-80% EtOAc/hexanos) produjo 0.9 g (62%) del compuesto del título como un sólido blanco. ^{1}H NMR (d_6-DMSO, δ 11.0, s, 1H; δ 7.95, d, 0.5H; δ 7.81, d, 0.5H; δ 7.65, s, 0.5H; δ 7.56, s, 0.5H; δ 7.46, d, 2H; δ 6.97, d, 2H; δ 6.96, br s, 2H; δ 4.19, m, 0.5H; δ 4.11, m, 0.5H; δ 3.77, m, 3H; δ 3.65, m, 1H; δ 3.48, m, 1H; δ 3.20, m, 2H; δ 1.75, m, 3H; δ 1.58, m, 2H; δ 1.42, s, 4.5H; δ 1.39, m, 1H; δ 1.36, s, 4.5H), LC/MS (APCI, ES, M+H=489).

2-[(Aminocarbonil)amino]-*N*-[(3*S*)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida; clorhidrato. A una solución agitada de *terc*-butil(3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino) azepan-1-carboxilato (0.9g, 1.8 mmol) en 1,4-dioxano (10 mL) se agregó 4.0N HCl en 1,4-dioxano (10 mL, 40 mmol). En poco tiempo se formó un precipitado y la reacción se agita durante 4 horas más a temperatura de la sala. Debido a la naturaleza higroscópica de la forma de la sal, el disolvente se retiró bajo vacío. El residuo se disolvió en metanol y se concentró bajo vacío (2x) para producir un sólido blancuzco. La recristalización usando 2-propanol produjo 0.45g (59%) de un sólido blanco. ^{1}H NMR (d_6-DMSO, δ 10.9, s, 1H; δ 9.58, br s, 1H; δ 9.29, br s, 1H; δ 8.39, d, 1H; δ 7.82, s, 1H; δ 7.48, d, 2H; δ 6.96, d, 2H; δ 4.36, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.20, m, 2H; δ 3.07, m, 1H; δ 1.98, m, 1H; δ 1.84, m, 4H; δ 1.59, m, 1H), LC/MS (APCI, ES, M+H=389).

Ejemplo 110

2-[(Aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida trifluoroacetato A una solución agitada de *terc*-butil(3S)-3-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil]carbonil}amino)piperidin-1-carboxilato disuelto en una pequeña

cantidad de metanol se agregó 4.0 N HCl en dioxano. La solución se agitó durante 1 hora a temperatura de la sala. El producto se purificó por Gilson (5% MeCN-H_2O→98%MeCN-H_2O) para producir 27 mg del compuesto del título como la sal trifluoroacetato. ^1H NMR (300MHz, d_3-MeOD; δ 7.55 (d, 2H), 7.45 (s, 1H), 7.05 (d, 2H), 4.35 (dd, 2H), 4.25 (m, 1H), 3.60 (dd, 2H), 3.50 (m, 1H), 3.30 (m, 5H), 2.95 (dd, 2H), 2.10 (dd, 2H), 1.80 (m, 2H), 1.35 (t, 6H)), LCMS, (ES, M+H=460).

Ejemplo 112

***terc*-Butil (3S)-3-{[(2-[(aminocarbonil)aminol-5-4-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato trifluoroacetato**

Metil {4-[2-(dietilamino)etoxi]fenil}acetato. A una solución de metil (4-hidroxifenil)acetato (16.6 g, 10 mmol) en DMF (100 mL) se agregó bromohidruro de 2-bromo-*N*,*N*-dietiletanamina (2.6 g, 10 mmol), Cs_2CO_3 (6.6g, 20 mmol). Luego de 1 hora se agregó un equivalente adicional del bromuro y, a continuación, se agitó de un día para otro a temperatura de la sala. La mezcla de reacción se vertió en un volumen más grande de agua fría. El producto se aisló luego por filtración y se purificó por cromatografía de columna (SiO_2, 10% MeOH/DCM) para producir 15.6 g del compuesto del título como un sólido blancuzco. LC/MS (APCI, ES, M+H=266).

{4-[2-(Dietilamino)etoxi]fenil}acetaldehído. A una solución agitada de metil{4-[2-(dietilamino)etoxi]fenil}acetato (5.3 g, 20 mmol) en tolueno anhidro (100 mL) enfriado a -78°C bajo N_2 se agregó hidruro de diisobutilaluminio (DIBAL, 1.0M en tolueno, 100 mL, 100 mmol) durante un período de 10-15 minutos. La mezcla se agitó a -78°C durante 2 horas más. La reacción se extinguió por la lenta adición de MeOH, seguido por la introducción de 10% de sal de Rochelle. La suspensión se diluyó con EtOAc y se agitó a temperatura de la sala durante 1 hora. La capa de EtOAc se reservó y la capa acuosa se extrajo con EtOAc (2x). Las capas

orgánicas se combinaron y se secaron sobre Na_2SO_4 y se filtraron. La solución se concentró bajo vacío para producir 4.7 g (100%) del aldehído del título como un semisólido viscoso amarillo, el cual se utilizó en el siguiente paso sin purificación. LC/MS (APCI, ES, M+H=236).

Metil 2-amino-5-{4-[2-(dietilamino)etoxi]fenil}tiofen-3-carboxilato. A una solución de {4-[2-(dietilamino)etoxi]fenil}acetaldehído (4.7 g, 20mmol) en DMF (30 mL) se agregó cianometil acetato (1.5 mL, 20 mmol) y azufre (0.6 g, 20 mmol), seguido por diisopropiletilamina (base de Hünig, 2.5 mL, 20 mmol). La suspensión resultante se volvió inmediatamente amarrillo oscuro a marrón con una exoterma. La mezcla de reacción se agitó de un día para otro a temperatura de la sala. La reacción se agregó lentamente a agua (~200 mL) agitando simultáneamente. Se formó un precipitado marrón claro y se filtró después de 30 minutos más de agitación. El sólido resultante se purificó por cromatografía de columna (SiO_2, 5-10% MeOH/DCM/0.5% NH_4OH) para producir 2.4 g del compuesto del título como un sólido amarillo claro. LC/MS (APCI, ES, M+H=349).

Ácido 2-amino-5-{4-[2-(dietilamino)etoxi]fenil}tiofen-3-carboxílico. A una solución agitada de metil 2-amino-5-{4-[2-(dietilamino)etoxi] fenil}tiofen-3-carboxilato (2.0 g, 5.7 mmol) en MeOH (50 mL) se agregó 6N NaOH (50 mL) y agua (50 mL). La reacción se calentó a reflujo durante 2 horas o hasta que el material de partida desapareció por TLC o LCMS. La solución se concentró bajo vacío a alrededor de la mitad del volumen original. Se ajustó el pH de la mezcla turbia resultante a 3-5 mediante la adición cuidadosa de 6N HCl (~150 mL) con agitación simultánea. El precipitado rojo con consistencia de goma se filtró y secó. La purificación se logró triturando en hexanos en ebullición. El producto (1.6 g) se aisló en forma pura por filtración luego de enfriar a temperatura de la sala y secar en un horno de vacío de un día para otro. LC/MS (APCI, ES, M+H=335).

terc-**Butil (3*S*)-3-{[(2-amino-5-{4-[2-(dietilamino)etoxi]fenil}-3-tienil) carbonil]amino}piperidin-1-carboxilato.** A una solución agitada de ácido 2-amino-5-{4-[2-(dietilamino)etoxi]fenil}tiofen-3-carboxílico (100 mg, 0.3 mmol) en DMF anhidro (2.0mL) se agrega *terc*-butil éster de ácido (S)-3-amino-azepan-1-carboxílico (60 mg, 0.3mmol), EDCI (63 mg, 0.33 mmol), HOBt (61 mg, 0.45 mmol), y NMM (0.04mL, 0.3 mmol). La mezcla de reacción se agitó de un día para otro a temperatura de la sala. La solución se diluyó con agua y EtOAc. La capa orgánica se separó y se reservó. La capa acuosa restante se extrajo con EtOAc(2x) y luego los extractos orgánicos combinados se agruparon y se lavaron con salmuera. La solución de EtOAc resultante se secó sobre Na_2SO_4, se filtró y se concentró bajo vacío para producir un sólido marrón. La purificación se llevó a cabo por Gilson (5% MeCN-H_2O→98%MeCN-H_2O) para producir 90 mg de un sólido blancuzco. LC/MS (APCI, ES, M+H=517).

terc-**Butil (3S)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino) etoxi] feny1}-3-tienil)carbonil]amino}piperidin-1-carboxilato.** A una solución agitada de *terc*-butil (3*S*)-3-{[(2-amino-5-{4-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato (90 mg, 0.17 mmol) en THF anhidro (5.0 mL) se agregó tricloroacetil isocianato (0.09 mL, 0.7 mmol) lentamente durante un período de 5 minutos. Una vez completa la adición, se formó un precipitado y la reacción se agitó durante 1 hora más. La mezcla de reacción se concentró en vacío. El residuo crudo se disolvió en metanol y luego se cargó con 2.0N NH_3 en metanol (0.35mL). La purificación por Gilson (5%MeCN-H_2O→98%MeCN-H_2O) produjo el compuesto del título (50 mg) como un sólido marrón claro. ^{1}H NMR (300MHz, d_3-MeOD; δ 7.55 (d, 2H), 7.45 (s, 1H), 7.05 (d, 2H), 4.35 (dd, 2H), 3.60-3.90 (m, 3H), 3.60 (dd, 2H), 3.30 (m, 4H), 2.95 (m, 2H), 1.90 (dd, 2H), 1.55 (m, 2H), 1.45 (s, 9H), 1.35 (t, 6H)), (APCI, ES, M+H=560).

Ejemplo 123

N-[(3S)-Azepan-3-il]-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida clorhidrato

Ácido 2-amino-5-(4-metoxi-fenil)-tiofen-3-carboxílico. A una solución agitada de éster metílico de ácido 2-amino-5-(4-metoxi-fenil)-tiofen-3-carboxílico (6.6 g, 26.6 mmol) en MeOH (200 mL) se agregó 6N NaOH (100 mL) y agua (50 mL). La reacción se calentó a reflujo durante 2 horas o hasta que el material de partida desapareció por TLC o LCMS. La solución se concentró bajo vacío a alrededor de la mitad del volumen original. Se ajustó el pH de la mezcla turbia resultante a 3-5 por la cuidadosa adición de 6N HCl (~150 mL) con agitación simultánea. El precipitado rojo con consistencia de goma se filtro y se secó. La purificación se logró triturando en hexanos en ebullición. El producto (6.0 g, 91%) se aisló en forma pura por filtración luego de enfriar a temperatura de la sala y secar en un horno de vacío de un día para otro. ^{1}H NMR (d_6-DMSO δ 7.37, d, 2H; δ 7.11, s, 1H; δ 7.10, br s, 2H; δ 6.94, d, 2H), LC/MS (APCI, ES, M+H=250).

Hidrazida de ácido pirazin-2-carboxílico. A una solución agitada de éster metílico de ácido pirazin-2-carboxílico (11.1 g, 80 mmol) en 140 mL de EtOH se agregó hidrato de hidrazina (15.6 mL, 320 mmol). La solución resultante se calentó a reflujo durante 2 horas. El disolvente se retiró bajo presión reducida y se secó bajo vacío elevado para producir la amida del título (11.1 g, 100%) como un sólido blanco. El producto se usó en los pasos subsiguientes sin purificación. ^{1}H NMR (d_6-DMSO δ 10.1, br s, 1H; δ 9.12, d, 1H; δ 8.83, d, 1H; δ 8.70, dd, 1H; δ 4.64, br s, 2H), LC/MS (APCI, ES, M+H=139).

Azida de pirazin-2-carbonilo. Hidracida de ácido pirazin-2-carboxílico (11.1 g, 80 mmol) se disolvió en 140 mL de agua y se cargó con 6N HCl (13.3 mL, 80 mmol) y se enfrió a 0°C. La mezcla de reacción agitada se

agregó lentamente a una solución de nitrito de sodio (8.3 g, 120 mmol) en 80 mL de agua durante un período de 15-30 minutos usando un embudo de adición. Una vez completa la adición la reacción se calentó a temperatura de la sala y se agitó durante 5 horas más. La solución se neutralizó por la cuidadosa adición de bicarbonato sódico ($NaHCO_3$) sólido y luego se extrajo con $CHCl_3$ (3x). Las fracciones orgánicas agrupadas se secaron sobre Na_2SO_4, se filtraron, se concentraron y se secaron bajo vacío elevado de un día para otro para producir 2.5 g (21%) de la azida de acilo del título. El producto se usó en pasos subsiguientes sin purificación. ^1H NMR (d_6-DMSO δ 9.30, d, 1H; δ 9.03, d, 1H; δ 8.90, dd, 1H).

***terc*-Butil éster de ácido (S)-3-{[2-amino-5-(4-metoxi-fenil)-tiofen-3-carbonil]-amino}-azepan-1-carboxílico.** A una solución agitada de ácido 2-amino-5-(4-metoxi-fenil)-tiofen-3-carboxílico (1.0 g, 4.0 mmol) en DMP anhidro (20 mL) se agrega *terc*-butil éster de ácido (S)-3-amino-azepan-1-carboxílico (1.03 g, 4.8 mmol), BOP (2.6 g, 6.0 mmol) y NMM (0.6 mL, 5 mmol). La mezcla de reacción se agitó de un día para otro a temperatura de la sala. La solución se diluyó con agua y EtOAc. La capa orgánica se separó y se reservó. La capa acuosa restante se extrajo con EtOAc (2x) y luego los extractos orgánicos combinados se agruparon y se lavaron con salmuera. La solución de EtOAc resultante se secó sobre Ka_2SO_4, se filtró y se concentró bajo vacío para producir un sólido marrón. La purificación se llevó a cabo por ISCO MPLC (SiO_2, 30-50% EtOAc/hexanos) para producir 0.9 g (50%) de un sólido blancuzco. ^1H NMR (d_6- DMSO δ 7.51, d, 0.5H; δ 7.46, s, 0.5H; δ 7.37, s, 0.5H; δ 7.36, d, 0.5H; δ 7.34, br s, 2H; δ 7.33, d, 2H; δ 6.93, d, 2H; δ 4.11, br s, 1H; δ 3.76, s, 3H; δ 3.61, dq, 1H; δ 3.47, m, 1H; δ 3.11, m, 2H; δ 1.73, m, 3H; δ 1.56, m, 2H; δ 1.42, s, 4.5H; δ 1.38, s+m, 5.5H;), LC/MS (APCI, ES, M+H=446).

***terc*-Butil (3*S*)-3-{[(5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}-3-tienil)carbonil]amino}azepan-1-carboxilato.** Una solución de *terc*-butil éster de ácido (S)-3-{[2-amino-5-(4-metoxi-fenil)-tiofen-3-

carbonil]-amino}-azepan-1-carboxílico (0.76 g, 1.7 mmol) y azida de pirazin-2-carbonilo (0.5 g, 3.4 mmol) en 20 mL de DME anhidro se hizo refluir durante 2 horas. El disolvente se retiró bajo presión reducida y el producto crudo se purificó usando ISCO MPLC (40-60% EtOAc/hexanos) para obtener 0.51 g (53%) del compuesto del título como un sólido amarillo claro. ^{1}H NMR (d_6-DMSO δ 12.5, br s, 0.5M; δ 12.4, br s, 0.5H; δ 10.90, s, 0.5H; δ 10.88, s, 0.5H; δ 8.93, s, 0.5H; δ 8.89, s, 0.5H; δ 8.33, d, 1H; δ 8.29, t, 1H; δ 8.05, d, 0.5H; δ 7.91, d, 0.5H; δ 7.74, s, 0.5H; δ 7.65, s, 0.5H; δ 7.52, dd, 2H; δ 7.00, d, 2H; δ 4.26, m, 0.5H; δ 4.17, m, 0.5H; δ 3.79, s, 3H; δ 3.69, m, 1H; δ 3.48, m, 1H; δ 3.21, m, 2H; δ 1.77, m, 3H; δ 1.61, m, 2H; δ 1.44, s, 4.5M; δ 1.38, s+m, 5.5H), LC/MS (APCI, BS, M+H=567).

***N*-[(3*S*)-Azepan-3-il]-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida; clorhidrato.** A una solución agitada de *terc*-butil (3*S*)-3-{[(5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}-3-tienil)carbonil]amino}azepan-1-carboxilato (0.51 g, 0.9 mmol) en 10 mL de MeOH se gragan 10 mL (40 mmol) de 4.0 N HCl en dioxano. La solución se agitó a temperatura de la sala durante 4 horas y luego se concentró bajo vacío. El residuo se recristalizó parcialmente triturando en 2-propanol a reflujo para producir el compuesto del título como un sólido anaranjado claro (0.30 g, 67%). ^{1}H NMR (d_6-DMSO δ 12.6, br s, 1H; δ 10.9, s, 1H; δ 9.55, br s, 1H; δ 9.24, br s, 1H; δ 8.88, s, 1H; δ 8.49, d, 1H; δ 8.35, dd, 1H; δ 8.29, d, 1H; δ 7.92, s, 1H; δ 7.54, d, 2H; δ 6.99, d, 2H; δ 4.42, m, 1H; δ 3.33, m, 1H; δ 3.23, m, 2H; δ 3.10, m, 1H; δ 2.02, m, 1H; δ 1.85, m, 4H; δ 1.62, m, 1H;), LC/MS (APCI, ES, M+H=467).

Ejemplo 136

2-[(Aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida trifluoroacetato

***terc*-Butil (3*S*)-3-{[(5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(hidroxiamino) carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato.** A una

solución de *terc*-butil (3*S*)-3-{[(2-amino-5-{4-[2-(dietilamino)etoxi]fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato (115 mg, 0.22 mmol) en THF (640 µL) se agregó 1,1'-carbonil diimidazol (178 mg, 1.1 mmol). La solución turbia resultante se agitó a temperatura de la sala durante 1 hora, luego de lo cual se agregaron clorhidrato de hidroxilamina (76.4 mg, 1.1 mmol) y Et_3N (100 µL) y la solución oscura resultante se agitó durante 48 horas a temperatura de la sala. La mezcla dividió en porciones entre EtOAc y H_2O y la capa orgánica se lavó con H_2O, salmuera y se secó ($MgSO_4$). La evaporación produjo un residuo amarillo. La purificación por Gilson (5%MeCN-H_2O→98% MeCN-H_2O) produjo la hidroxi urea del título.

5-{4-[2-(Dietilamino)etoxi]fenil}-2-{[(hidroxiamino)carbonil] amino}-*N*-[(3*S*)-piperidin-3-il]tiofen-3-carboxamida. Una solución agitada de *terc*-butil (3*S*)-3-{[(5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(hidroxiamino) carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato en dioxano se trató con 4.0N de solución de HCl en dioxano (3 mL) y la mezcla turbia resultante se agitó a temperatura de la sala durante 1 hora. La evaporación del disolvente produjo 5-[4-(2-dietilamino-etoxi)-fenil]-2-(3-hidroxi-urea)-tiofen-3-ácido carboxílico-(S)-piperidin-3-ilamida como la sal clorhidrato (8 mg). ^1H NMR (300MHz, DMSO-d_6) δ ppm 1.17-1.40 (m, 6 H) 1.54-1.81 (m, 2H) 1.84-2.07 (m, 2H) 2.76-2.99 (m, 2H) 3.05- 3.25 (m, 4 H) 3.41-3.61 (m, 4H) 3.73-3.88 (m, 1H) 4.29-4.42 (m, 1H) 4.40-4.64 (m, 1H) 5.86 (s, 1H) 7.07 (d, *J*=8.48 Hz, 2H) 7.55 (d, *J*=8.48 Hz, 2H) 7.82 (s, 1H) 9.44 (s, 1H) 9.65 (s, 1H); LC/MS (ES, M+H=476).

Ejemplo 137

2[(Aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(3-metoxifenil)tiofen-3-carboxamida

***terc*-Butil (3*S*)-3-[({2-[(aminocarbonil)amino]-5-bromo-3-tienil} carbonil)amino]azepan-1-carboxilato**

A una solución de metil 2-[(aminocarbonil)amino]-5-bromotiofen-3-carboxilato (1 equiv.) en THF seco (0.3 M) se agregó una solución de [Me_2Al-Boc-3-(S)-aminohomopiperidina] (2 equiv.) en THF (1.0 M) (la cual se preformó por la adición de Me_3Al (2.0 M en hexanos) a una solución de Boc-3-(S)-homopiperidina en THF a -78°C y la solución amarilla resultante se calentó a temperatura de la sala y se agitó durante 15 minutos más) y la solución amarillo profundo resultante se agitó de un día para otro a temperatura de la sala. La mezcla de reacción se enfrió con hielo y se agregó lentamente 10% de una solución acuosa de sal de Rochelle para extinguir la reacción. La solución bifásica resultante se calentó a temperatura de la sala y se agitó durante 1 hora más. La mezcla se diluyó con EtOAc y H_2O, la capa acuosa se extrajo con EtOAc (3x) y los extractos orgánicos combinados se lavaron con H_2O, salmuera y se secaron ($MgSO_4$). La evaporación produjo un sólido anaranjado pálido. La purificación por cromatografía de columna (40-60% EtOAc/hexanos) produjo un sólido blanco. LC/MS (ES, M+H=462).

***terc*-Butil (3S)-3-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil] carbonil}amino)azepan-1-carboxilato.** Un matraz cargado con *terc*-butil(3S)-3-[({2-[(aminocarbonil)amino]-5-bromo-3-tienil} carbonil)amino]azepan-1-carboxilato (1.0 mmol), ácido 3-metoxifenilbórico (1.5 mmol), Cs_2CO_3 (3.0 mmol) y Pd (PPh_3)$_4$ (0.05-0.1 mmol) y se purgó con nitrógeno durante 10 minutos. Se agregaron dioxano (4mL) y H_2O (1mL) bajo una atmósfera de nitrógeno y la mezcla resultante se calentó a 90°C durante 2-4 horas. La mezcla se dejó enfriar a temperatura de la sala y la mezcla se filtró (0.45 uM o tierra de diatomeas). La capa acuosa se separó y el disolvente restante se concentró a sequedad. El residuo se purificó por cromatografía de columna (SiO_2) en un sistema de separación MPLC ISCO (30-60% EtOAc/hexanos) para producir un sólido blancuzco. LCMS, (ES, M+H=489).

2-[(Aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(3-metoxifenil)tiofen-3-carboxamida clorhidrato. A una solución agitada de *terc*-butil (3*S*)-3-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil] carbonil}amino)azepan-1-carboxilato disuelto en una pequeña cantidad de metanol se agregó 4.0 N HCl en dioxano. La solución se agitó durante 1 hora a temperatura de la sala. El producto como la sal clorhidrato se obtuvo como un sólido blancuzco luego del retiro del disolvente y secamiento. ^{1}H NMR (d_6-DMSO δ 10.90 (s, 1H), 9.21 (s, 1H), 9.01 (s, 1H), 8.29 (d, 1H), 7.93 (s, 1H), 7.29 (t, 1H), 7.11 (d, 2H), 7.03 (s, 1H), 6. 83 (d, 1H), 4.33 (s, 1H), 3.81 (s, 3H), 3.20 (m, 4H), 2.00 (m, 1H), 1.84 (m, 4H), 1.56 (m, IH)), LCMS, (ES, M+H=389).

Ejemplo 139

2-[(Aminocarbonil)amino]-5-(3-metoxifenil)-N-[(3S)-piperidin-3-il] tiofen-3-carboxamida

Metil 2-({[(tricloroacetil)amino]carbonil}amino)tiofen-3-carboxilato. A una solución agitada éster metílico de ácido de 2-amino-tiofen-3-carboxílico (1 eq.) en THF (mL) anhidro se agregó lentamente tricloroacetil isocianato (1 eq.) durante un período de 5 minutos. Una vez completa la adición, se formó un precipitado y la reacción se agitó durante 1 hora más. El producto deseado se obtuvo por filtración para producir metil 2-({[(tricloroacetil)amino]carbonil}amino)tiofen-3-carboxilato (99%) como un sólido blancuzco. El producto se utilizó en el siguiente paso sin purificación posterior de ningún tipo. LC/MS (ES, M+H=345).

Metil 5-bromo-2-({[(tricloroacetil)amino]carbonil}amino)tiofen-3-carboxilato. A una solución agitada de metil 2-({[(tricloroacetil)amino] carbonil}amino)tiofen-3-carboxilato (1 eq.) en ácido acético glacial (20 mL) se agregó lentamente una solución de bromo (1.3 eq.) en ácido acético glacial (5 mL) durante un período de 5 minutos. Una vez completa la adición, la solución oscura resultante se agitó durante 30 minutos a

temperatura de la sala. El disolvente se evaporó bajo vacío y el residuo se trituró con H_2O. Se obtuvo el compuesto del título por filtración (99%) como un sólido blancuzco. El producto se utilizó en el siguiente paso sin purificación posterior de ningún tipo luego de secar durante 2 días bajo P_2O_5. LC/MS (ES, M+H=425).

Metil 2-[(aminocarbonil)amino]-5-bromotiofen-3-carboxilato. Una solución agitada de metil 5-bromo-2-({[(tricloroacetil)amino]carbonil} amino)tiofen-3-carboxilato (1 eq.) en metanol anhidro se purgó con amoníaco seco durante 20 minutos. Luego de agitar durante 10 minutos más a temperatura de la sala, se observó precipitación y el producto se aisló por filtración (rendimiento 100%). LC/MS (ES, M+H=280).

***terc*-Butil (3S)-3-[({2-[(aminocarbonil)amino]-5-bromo-3-tienil} carbonil)amino]piperidin-1-carboxilato.** A una solución de metil 2-[(aminocarbonil)amino]-5-bromotiofen-3-carboxilato (1 equiv.) en THF seco (0.3 M) se agregó una solución de [Me_2Al-Boc-3-(S)-aminopiperidina] (2 equiv.) en THF (1.0M) (la cual se preformó por la adición de Me_3Al (2.0M en hexanos) a una solución de Boc-3-(S)-piperidina en THF a -78°C y la solución amarilla resultante se calentó a temperatura de la sala y se agitó durante 15 minutos más) y la solución amarillo profundo se agitó de un día para otro a temperatura de la sala. La mezcla de reacción se enfrió con hielo y se agregó lentamente 10% de una solución acuosa de sal de Rochelle para extinguir la reacción. La solución bifásica resultante se calentó a temperatura de la sala y se agitó durante 1 hora más. La mezcla se diluyó con EtOAc y H_2O, la capa acuosa se extrajo con EtOAc (3x) y los extractos orgánicos combinados se lavaron con H_2O, salmuera y se secaron ($MgSO_4$). La evaporación produjo un sólido anaranjado pálido. La purificación por cromatografía de columna (40-60%EtOAc/hexanos) produjo un sólido blanco. ^1H NMR (d_6-DMSO, δ 10.9, s, 1H; δ 9.48, br s, 1H; δ 9.31, br s, 1H; δ 8.48, d, 1H; δ 8.10, s, 1H; δ 7.57, d, 2H; δ 7.38, t, 2H; δ 7.23, t, 1H; δ 7.01, br s, 2H; δ 4.26, m, 1H; δ

3.29, m, 1H; δ 3.11, m, 1H; δ 2. 94, m, 2H; δ 1.91, m, 2H; δ 1.69, m, 2H), LC/MS (APCI, ES, M+H=345).

***terc*-Butil (3S)-3-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato.** Se cargó un matraz con *terc*-butil (3S)-3-[({2-[(aminocarbonil)amino]-5-bromo-3-tienil} carbonil) amino]piperidin-1-carboxilato (1.0 mmol), ácido 3-metoxifenilbórico (1.5 mmol), Cs_2CO_3 (3.0 mmol) y Pd $(PPh_3)_4$ (0.05-0.1 mmol) y se purgó con nitrógeno durante 10 minutos. Se agregaron dioxano (4 mL) y H_2O (1 mL) bajo atmósfera de nitrógeno y la mezcla resultante se calentó a 90°C durante 2-4 horas. La mezcla se dejó enfriar a temperatura de la sala y la mezcla se filtró (0.45 uM o tierra de diatomeas). La capa acuosa se separó y el disolvente restante se concentró a sequedad. El residuo se purificó por cromatografía de columna (SiO_2) en un sistema de separación MPLC ISCO (30-60% EtOAc/hexanos) para producir un sólido blancuzco. LCMS, (ES, M+H=475).

2-[(Aminocarbonil)amino]-5-(3-metoxifenil)-N-[(3S)-piperidin-3-il] tiofen-3-carboxamida clorhidrato. A una solución agitada de *terc*-butil (3*S*)-3-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil]carbonil} amino)piperidin-1-carboxilato disuelto en una pequeña cantidad de metanol se agregó 4.0 N HCl en dioxano. La solución se agitó durante 1 hora a temperatura de la sala. El producto como la sal clorhidrato se obtuvo como un sólido blancuzco luego de retirar el disolvente y secar. ^{1}H NMR (d_6-DMSO δ 10.94 (s, 1H), 9.41 (s, 1H), 9.19 (s, 1H), 8.47 (d, 1H), 8.11 (s, 1H), 7.30 (t, 1H), 7.15 (d, 1H), 7.05 (br,2H), 6.84 (d, 1H), 4.25 (s, 1H), 3.82 (s, 3H), 3.29 (d, 1H), 3.12 (d, 1H), 2.97 (m, 2H), 1.92 (d, 2H), 1.69 (m, 2H)). LCMS, (ES, M+H=375).

Otros Ejemplos

Ejemplos **1-3, 5-25, y 27-109** se prepararon en una forma similar a la descrita para ejemplos **4 y 26.**

Ejemplos **111** y **113-115** se prepararon en una forma similar a la descrita para ejemplos **110** y **112**.

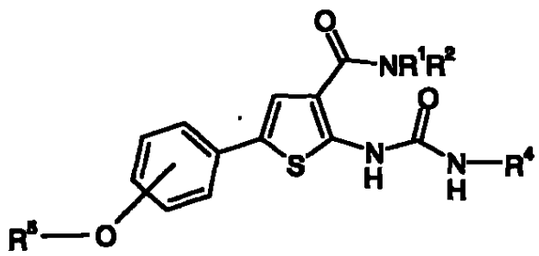
Ejemplos **116-119** se prepararon de acuerdo con el **Esquema V** general.

Ejemplos **121-122** y **124-135** se prepararon en una forma similar a la descrita para ejemplos **123** y **136**.

Ejemplos **138** y **140** se prepararon en una forma similar a la descrita para ejemplos **137** y **139**.

Reivindicaciones

1. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o precursores hidrolizables *in vivo*:



(I)

en donde:

R^1 y R^2 en cada ocurrencia se seleccionan independientemente de H, opcionalmente sustituido C_{1-6}alquilo, o heterociclilo opcionalmente sustituido; con la condición que R^1 y R^2 no son ambos H; ó R^1 y R^2 y el N, al cual se unen, forman en combinación heterociclilo opcionalmente sustituido;

R^4 se selecciona de H, OH, carbociclilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido;

R^5 se selecciona de H, carbociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido.

2. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^2, R^4, y R^5 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^1 es un heterociclilo opcionalmente sustituido.

3. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^2, R^4, y R^5 tienen cualquiera de los significados definidos en la

reivindicación 1 y R^1 es un heterociclilo opcionalmente sustituido en donde 1, 2, ó 3 sustituyentes se selecciona/seleccionan de halógeno, nitro, amino, ciano, trifluorometilo, alquilo, alquenilo, alquinilo, haloalquilo, alcoxi, hidroxi, alquilhidroxi, carbonilo, -CH(OH)CH_3, -CH_2NH-alquil-OH, alquil-(OH)CH_3, -CH_2-fenil-(OCH_3)$_2$, -Oalquilo, -OCH_3, -Ofenilo, -OCOalquilo, -NHCHO, -Nalquilo, -N-(alquil)-CHO, -NH-CO-amino, -N-(alquil)-CO-amino, -NH-COalquilo, -N-(alquil)-COalquilo, -carboxi, -amidino, -CO-amino, -CO-alquilo, -CO_2alquilo, mercapto, -Salquilo, -SCH_2furanilo, -SO(alquil), -SO_2(alquil), -SO_2- amino, -alquilsulfonilamino, fenilo, anisol, dimetoxifenilo, trimetoxifenilo, halofenilo, cicloalquilo, heterociclilo, -alquil-NH-cicloalquilo, -alquil-NH-heterociclilo, -alquil-NH-alquil-OH, -C(=O)OC(CH_3)$_3$, -N(CH_3)$_2$, -N(CH_2CH_3)$_2$, -alquil-NH-alquil-heterociclilo, -alquil-arilo, -metil-fenilo, alquil-policiclilo, alquil-amino, alquil-hidroxi, -CH_2NH-alquil-heterociclilo, -CH_2NHCH_2CH(CH_3)$_2$, vicinal -O(alquil)O-, vicinal -OC(haloalquil)O-, vicinal –CH_2O(alquil)O-, vicinal -S(alquil)S- y -O(alquil)S-.

4. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^2, R^4, y R^5 tienen cualquiera de los significados definidos en la reivindicación 1 y R^1 es un heterociclilo opcionalmente sustituido en donde 1, 2, ó 3 sustituyentes se selecciona/seleccionan de: -OH, C(=O)OC(CH_3)$_3$, NH_2, C_{1-6}alquilo, metoxibenceno, o dimetoxi benceno.

5. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^2, R^4, y R^5 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^1 es un heterociclilo en donde heterociclilo se selecciona de piperdinilo, piridinilo, pirrolidinilo, pirazinilo, azepanilo, azetidinilo, azabiciclozinilo, furanilo, tienilo.

6. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^1, R^4, y R^5 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^2 es H.

7. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^1, R^2, y R^5 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^4 es H.

8. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^1, R^2, y R^4 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^5 es H o un C_{1-6}alquilo opcionalmente sustituido.

9. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^1, R^2, y R^4 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^5 es H o un alquilo opcionalmente sustituido en donde 1, 2 ó 3 sustituyentes se selecciona/seleccionan independientemente de: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH_3, OH, -C_{1-6}alquilo, morfolino, piperidinilo, pirrolodinilo.

10. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^1, R^2, y R^4 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^5 es H ó un C_{1-3}alquilo opcionalmente sustituido.

11. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^1, R^2, y R^4 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^5 es H ó un C_{1-3}alquilo opcionalmente sustituido en donde 1, 2 ó 3 sustituyentes se selecciona/seleccionan de: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH_3, OH, -C_{1-6}alquilo, morfolino, piperidinilo, pirrolodinilo.

12. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, como se declara en la reivindicación 1, en donde:

R^1 es un heterociclilo opcionalmente sustituido;

R^2 es H;

R^4 es H;

R^5 es H ó C_{1-6}alquilo opcionalmente sustituido.

13. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, como se declara en la reivindicación 1, en donde:

R^1 es un heterociclilo opcionalmente sustituido en donde el sustituyente se selecciona de uno o más de los siguientes: -NH_2, C_{1-6}alquilo, -$C(=O)OC(CH_3)_3$,

R^2 es H;

R^4 es H;

R^5 es H ó un C_{1-6}alquilo opcionalmente sustituido en donde el sustituyente se selecciona de uno o más de los siguientes: -C_{1-6}alquilo, -$N(C_{1-3}alquil)_2$.

14. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, como se declara en la reivindicación 1, en donde:

R^1 es un heterociclilo opcionalmente sustituido en donde el sustituyente se selecciona de uno o más de los siguientes: $-NH_2$, C_{1-6}alquilo, $-C(=O)OC(CH_3)_3$,

R^2 es H;

R^4 es H;

R^5 es H ó un C_{1-3}alquilo opcionalmente sustituido en donde 1, 2 ó 3 sustituyentes se selecciona/seleccionan de: NH_2, $NHCH_3$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, OCH_3, OH, $-C_{1-6}$alquilo, morfolino, piperidinilo, pirrolodinilo.

15. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, como se declara en la reivindicación 1, en donde:

R^1 es un heterociclilo;

R^2 es H;

R^4 es H;

R^5 es H ó un C_{1-6}alquilo.

16. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo*, como se declara en la reivindicación 1, en donde:

R^1 es un heterociclilo de 6 miembros que contiene por lo menos un N en el anillo;

R^2 es H;

R^4 es H;

R^5 es un C_{1-3}alquilo.

17. Un compuesto de fórmula (I) seleccionado de:

terc-butil 3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;

terc-butil 3-{[(2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[(3R)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida;

N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{4-[2-(dietilamino)etoxi]fenil}-2-tienil)urea;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(2-aminoetil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1-metilpiperidin-4-il)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilazepan-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-[3-(hidroximetil)fenil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-piridin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-1-metilpiperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{3-[2-(dietilamino)etoxi]fenil}-N-pirrolidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-pirrolidin-3-il] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[2-(dimetilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[2-(dietilamino)etil]-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piperidin-4-ilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-pirrolidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(1-etilpiperidin-3-il)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[(3S)-1-etilazepan-3-il]-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(3-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

terc-butil(3S)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil]carbonil}amino)pirrolidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-piperidin-3-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(1-bencilpiperidin-4-il)-5-(4-metoxifenil) tiofen-3-carboxamida;

terc-butil 3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-[4-(2-piperidin-1-iletoxi)fenil]-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-azetidin-3-il-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(2S)-pirrolidin-2-ilmetil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-pyndin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperidin-1-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-1-azabiciclo[2.2.2]oct-3-il-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(2-hidroxietil)-5-(4-hidroxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(trans-4-hidroxiciclohexil)-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piperazin-1-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-4-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-3-iletil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2,2,6,6-tetrametilpiperidin-4-il)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(2-metoxifenil)-N-piperidin-4-iltiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(tetrahidrofuran-2-ilmetil) tiofen-3-carboxamida;

terc-butil (3R)-3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-3-ilmetil)tiofen-3-carboxamida;

terc-butil 3-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)azetidin-1-carboxilato;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-4-ilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(3-metoxipropil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida;

N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]urea;

2-[(aminocarbonil)amino]-N-(2-metoxietil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-(2-tienilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-{2-[(2-furilmetil)tio]etil}-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-hidroxifenil)-N-[2-(2-tienil)etil]tiofen-3-carboxamida;

N-(3-[(4-aminopiperidin-1-il)carbonil]-5-{3-[2-(dietilamino)etoxi]fenil}-2-tienil)urea;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(3R)-piperidin-3-ilmetil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(1,2,3,4-tetrahidroquinolin-3-il)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(1,3-benzodioxol-5-ilmetil)-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(3-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-[2-(3,4-dimetoxifenil)etil]-5-(4-metoxifenil) tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-[(5-metil-2-furil)metil] tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(piridin-2-ilmetil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-N-(4-fluorobencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

terc-butil4-({[2-[(aminocarbonil)amino]-5-(3-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-N-(2-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-fenoxietil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-(4-metoxifenil)-N-(2-piridin-2-iletil)tiofen-3-carboxamida;

terc-butil4-({[2-[(aminocarbonil)amino]-5-(4-metoxifenil)-3-tienil] carbonil}amino)piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-N-(4-metoxibencil)-5-(4-metoxifenil)tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;

2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi]fenil}-N-[(3R)-piperidin-3-il]tiofen-3-carboxamida;

terc-butil(3S)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-{4-[2-(dietilamino)etoxi] fenil}tiofen-3-carboxamida;

terc-butil (3R)-3-{[(2-[(aminocarbonil)amino]-5-{4-[2-(dietilamino)etoxi] fenil}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

N-[3-{[(3S)-3-aminoazepan-1-il]carbonil}-5-(4-metoxifenil)-2-tienil]urea;

5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

5-{3-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;

5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

N-[(3S)-azepan-3-il]-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}tiofen-3-carboxamida;

5-{3-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

N-(2-aminoetil)-5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida;

5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-3-il-2-{[(pirazin-2-ilamino) carbonil]amino}tiofen-3-carboxamida;

5-(4-metoxifenil)-N-piperidin-4-il-2-{[(pirazin-2-ilamino)carbonil]amino} tiofen-3-carboxamida;

terc-butil 3-{[(5-{3-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino) carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato;

5-{4-[2-(dietilamino)etoxi]fenil}-N-piperidin-4-il-2-{[(pirazin-2-ilamino)

carbonil]amino}tiofen-3-carboxamida;
5-(4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil]amino}-N-[(3S)-pirrolidin-3-il]tiofen-3-carboxamida;
N-[3-(1,4-diazepan-1-ilcarbonil)-5-(4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea;
N-[3-[(3-aminopirrolidin-1-il)carbonil]-5-(4-metoxifenil)-2-tienil]-N'-pirazin-2-ilurea;
terc-butil 4-{[(5-[4-metoxifenil)-2-{[(pirazin-2-ilamino)carbonil] amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato;
terc-butil 3-[(5-{4-[2-(dietilamino)etoxi]fenil}-2-{[(pirazin-2-ilamino) carbonil]amino}-3-tienil)carbonil]amino}piperidin-1-carboxilato;
5-[4-(2-dietilamino-etoxi)-fenil]-2-(3-hidroxi-urea)-tiofen-3-ácido carboxílico-(S)-piperidin-3-ilamida;
2-[(aminocarbonil)amino]-N-[(3S)-azepan-3-il]-5-(3-metoxifenil)tiofen-3-carboxamida;
2-[(aminocarbonil)amino]-5-(2-hidroxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;
2-[(aminocarbonil)amino]-5-(3-metoxifenil)-N-[(3S)-piperidin-3-il]tiofen-3-carboxamida;
2-[(aminocarbonil)amino]-5-[2-(benciloxi)fenil]-*N*-[(3S)-piperidin-3-il] tiofen-3-carboxamida.

18. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable como se declara en una cualquiera de las reivindicaciones 1 a 17 para uso como medicamento.

19. El uso de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable como se declara en una cualquiera de las reivindicaciones 1 a 17, en la manufactura de un medicamento para el tratamiento o profilaxis de trastornos asociados con cáncer.

20. Un método para el tratamiento de cáncer, que comprende administrar a un humano una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17.

21. Un método para el tratamiento de cáncer de mama, cáncer colorrectal, cáncer ovárico, cáncer de pulmón (amicrocítico), tumores cerebrales malignos, sarcomas, melanoma y linfoma administrando un compuesto de fórmula I o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17.

22. Un método de tratar cáncer administrando a un humano un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17 y un agente anti-neoplásico.

23. Un método de tratar cáncer administrando a un humano un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17 y un agente que tiene como objetivo la destrucción del ADN.

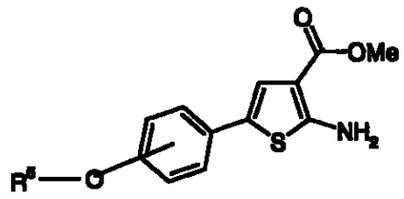
24. Un método para el tratamiento de infecciones asociadas con cáncer, que comprende administrar a un anfitrión, necesitado de tal tratamiento, una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17.

25. Un método para el tratamiento profiláctico de infecciones asociadas con cáncer, que comprende administrar a un anfitrión, necesitado de tal tratamiento, una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17.

26. Una composición farmacéutica que comprende un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, como se define en una cualquiera de las reivindicaciones 1 a 17, junto con por lo menos un vehículo, diluyente o excipiente farmacéuticamente aceptable.

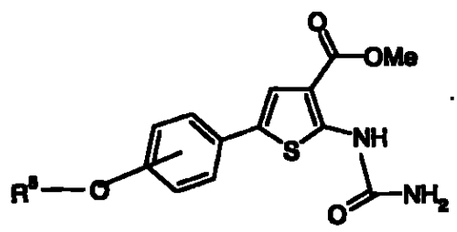
27. Un proceso para la preparación de un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o precursores hidrolizables *in vivo*, como se define en una cualquiera de las reivindicaciones 1 a 17, que comprende:

(a) la reacción de un 2-aminotiofeno mostrado a continuación como Fórmula II



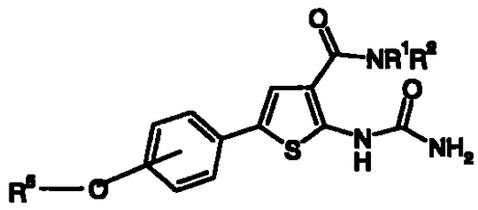
II

en donde el hidrógeno en la posición 2-amino se desplaza para formar una amida, mostrada como fórmula III a continuación



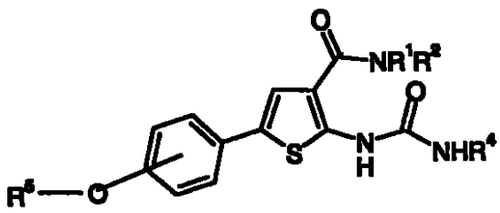
III

en donde el éster de metilo se convierte en una amida utilizando la amina deseada en conjunción con un complejo organometálico de aluminato, para obtener el producto mostrado como fórmula IV a continuación:



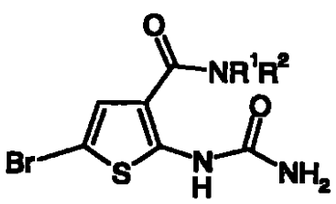
IV

en donde la amida se convierte en varias ureas secundarias sustituidas por la reacción con diferentes isocianatos para obtener el producto mostrado como fórmula V a continuación:



V

28. El uso de un compuesto de la siguiente fórmula (VI) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* en la manufactura de un compuesto de fórmula (I) como se expone en una cualquiera de las reivindicaciones 1-17.



VI

AS: 100478
CLO
201

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GLOBAL INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje
SUEDE

RECEIVED
21 JUL 2005
ASTRA ZENECA PLC
GLOBAL INTELLECTUAL

PCT

CODE	DATE	NTD

ANKOM 18 JUL 2005 GIPS

DATA ENTERED

FINAL CHECK

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing (day/month/year): 15.07.2005

Applicant's or agent's file reference: 101084-1 WO

IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2004/003473	12.08.2004	15.08.2003

Applicant
ASTRAZENECA AB

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Brell, S

Tel. +49 89 2399-7271

CODE	DATE	NTD
ANKOM 18 JUL 2005		GIPS
DATA ENTERED		
FINAL CHECK		

202

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 101064-1 WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/GB2004/003473	International filing date *(day/month/year)* 12.08.2004	Priority date *(day/month/year)* 15.08.2003
International Patent Classification (IPC) or national classification and IPC C07D333/38, C07D409/12, A61K31/38, A61P35/00		
Applicant ASTRAZENECA AB		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.06.2005	15.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bakboord, J Telephone No. +49 89 2399-

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

204 203

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003473

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-79 as originally filed

   Claims, Numbers

   1-28 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/GB2004/003473

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-25

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 20-25

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5, 7, 9, 11-17
	No:	Claims	1, 6, 8, 10, 18-27, 28
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-19, 26-28
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The present application relates to 2-ureido-3-amido-5-phenyl substituted thiophenes and their use as checkpoint kinase 1 inhibitors.

V.2 Reference is made to the following documents:

D1: WO 03/029241 A
D2: WO 03/028731 A
D3: WO 02/070494 A

V.3 Novelty

Document D1 discloses a compound of formula I in which R^1 is hydrogen, R^2 is methyl, R^4 is methyl and R^5 is methyl (example 28). Moreover document D1 discloses 2-ureido-3-amido-5-phenyl substituted thiophenes and their use as checkpoint kinase 1 inhibitors (claim 5).
Document D1 also discloses the use of a compound of formula VI in the manufacture of a compound of formula I (scheme II).
Document D2 discloses 2-amido-3-ureido-5-phenyl substituted thiophenes and their use as checkpoint kinase 1 inhibitors (claim 6).
Document D3 discloses phenyl rings substituted with groups $C(O)NR^1R^2$, $N(H)C(O)N(H)R^4$ and OR^5 (see e.g. compounds 1-6) to be used as checkpoint kinase 1 inhibitors.

A compound of formula I for the use as checkpoint inhibitors is disclosed in document D1. Claims 1, 6, 8, 10, 18-27 therefore do not fulfill the requirements of

Article 33(2) PCT.

A compound of formula I as described in claims 2-5, 7, 9, 11-17 is disclosed in none of the documents. These claims therefore fulfill the requirements of Art 33(2) PCT.

The use of a compound of formula VI for the manufacture of a compound of formula I is disclosed in document D1. Claim 28 therefore does not fulfill the requirements of Art 33(2) PCT.

V.4 Inventive step

As the use of thiophene 2-ureido-3-amido-5-phenyl substituted thiophenes for the inhibition of checkpoint kinase 1 is known from document D1 the present application cannot be considered to involve an inventive step (Art 33(3) PCT).

V.5 Industrial applicability

For the assessment of the present claims 20-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

TRATADO SOBRE CO PERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

Remitente:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:	**PCT**
GLOBAL INTELLECTUAL PROPERTY AstraZeneca AB SE- 151 85 Södertälje SUECIA	**COMUNICACIÓN SOBRE EL ENVÍO DEL INFORME DE EXAMEN PRELIMINAR INTERNACIONAL** (Regla 71.1 PCT)

	Fecha de envío *(Día/Mes/Año)* 15.07.2005
No. de Expediente del Solicitante o Apoderado 101064-1 WO	**COMUNICACIÓN IMPORTANTE**

No. de Solicitud Internacional	Fecha Internacional de Presentación *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT/GB2004/003473	12.08.2004	15.08.2003

Solicitante

ASTRAZENECA AB

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.

2. Una copia del informe, en caso dado con los anexos correspondientes se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.

3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4. **RECORDATORIO**

   Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

   Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

   Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

   Se llama la atención del solicitante al Artículo 33(5), que establece que los criterios de novedad, actividad inventiva y posibilidad de aplicación industrial descritos en Artículo 33(2) a (4) sirven meramente los propósitos del examen preliminar internacional y que "todo Estado Contratante puede aplicar criterios adicionales o diferentes para efectos de decidir si la invención reivindicada es patentable o no" (véase también Artículo 27 (5)). Los criterios adicionales pueden incluir, por ejemplo, exención de patentabilidad y los requerimientos, si se permite la divulgación, y de claridad y soporte de las reivindicaciones.

Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional	Empleado Autorizado
Oficina Europea de Patentes D-80298 Munich Tel.: +49 89 2399 – 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	**Breil, S** Tel.: +49 89 2399-7271

Formulario PCT/IPEA/416 (Enero 2004)

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TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Capítulo II del Tratado de Cooperación en Materia de Patentes)

(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado	PROCEDIMIENTO POSTERIOR	Véase formulario PCT/IPEA/416
101064-1 WO		
No. Solicitud Internacional	**Fecha Internacional de Presentación** *(día/mes/año)*	**Fecha de Prioridad** *(día/mes/año)*
PCT/GB2004/003473	12.08.2004	15.08.2003

Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC

C07D333/38, C07D409/12, A61K31/38, A61P35/00

Solicitante

ASTRAZENECA AB

1. El presente informe es el informe de examen preliminar internacional, establecido por esta Oficina Encargada del Examen Preliminar Internacional bajo Artículo 35 y transmitido a solicitante de acuerdo con el Artículo 36.
2. El presente INFORME comprende un total de 6 hojas, inclusive esta portada
3. Este importe se acompaña igualmente por ANEXOS, que comprenden:
   a. ☐ *(enviado al solicitante y a la Oficina Internacional)* un total de hojas, como sigue:
      ☐ hojas de la descripción, reivindicaciones y/o dibujos que se han corregido y constituyen la base de el presente informe y/o hojas que contienen rectificaciones autorizadas por esta Oficina (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas).
      ☐ hojas que reemplazan hojas anteriores, pero que esta Oficina considera que contienen una corrección que va más allá de la divulgación en la solicitud internacional tal como se presentó, como se indica en el ítem 4 de Cuadro No. I y el Cuadro Adicional.
   b. ☐ (enviado a la Oficina Internacional únicamente) un total de (indicar tipo y número de medios electrónicos)) ,que contiene un listado de secuencias y/o tablas relacionadas con este asunto, en formato de lectura por computador únicamente, como se indica en el Cuadro Adicional Relativo al Listado de Secuencias (véase Sección 802 de las Instrucciones Administrativas).
4. El presente informe contiene datos con respecto a los siguientes puntos:
   - ☒ Cuadro No. I Base del Informe
   - ☐ Cuadro No. II Prioridad
   - ☒ Cuadro No. III Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial
   - ☐ Cuadro No. IV Uniformidad deficiente de la invención
   - ☒ Cuadro No. V Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración
   - ☐ Cuadro No. VI Ciertos documentos enumerados
   - ☐ Cuadro No. VII Ciertas deficiencias del registro internacional
   - ☐ Cuadro No. VIII Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición	Fecha de la preparación de el presente informe
02.06.2005	15.07.2005
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional	**Empleado Autorizado**
Oficina Europea de Patentes D-80298 Munich Tel.: +49 89 2399 – 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Bakboord, J Teléfono No.: +49 89 2399-

Formulario PCT/IPEA/409 (portada) (Enero 2004)

Cuadro No. I Base del informe

1. En lo concerniente al **idioma:** El presente informe se basa en la solicitud internacional en el idioma en el cual se presentó, salvo indicación en contrario consignada bajo este punto.

   ☐ El presente informe se basa en traducciones del idioma original al siguiente idioma, que es el idioma de una traducción suministrada para los efectos de:
   - ☐ la búsqueda internacional (según las reglas 12.3 y 23.1 (b))
   - ☐ la publicación de la solicitud internacional (según la regla 12.4).
   - ☐ el examen preliminar internacional (según las reglas 55.2 y/o 55.3).

2. Con respecto a los **elementos*** de la solicitud internacional, este informe se basa en *(hojas intercambiables que se han suministrado a la oficina receptora en respuesta a una invitación bajo Artículo 14 se tienen en este informe por "presentadas originalmente" y no se anexan a este informe):*

   Descripción, páginas

   1-79 versión original

   Reivindicaciones, No.

   1-28 versión original

   ☐ Un listado de secuencias y/o cualquier tabla(s) relacionada(s)– véase Cuadro Adicional relativo al Listado de Secuencias

3. ☐ Las correcciones han resultado en la cancelación de:
   - ☐ la descripción, páginas
   - ☐ las reivindicaciones, Nos.
   - ☐ los dibujos, hojas/figs.
   - ☐ el listado de secuencias *(especificar)*:
   - ☐ cualquier tabla(s) relacionada con el listado de secuencias *(especificar)*:

4. ☐ El presente informe se preparó como si no se hubieran hecho (algunas de) las correcciones anexadas a este informe y enumeradas a continuación ya que éstas, por las razones aducidas, en concepto de la oficina van más allá del contenido de divulgación en la versión presentada originalmente (Regla 70.2 (c)).
   - ☐ la descripción, páginas:
   - ☐ las reivindicaciones, Nos.
   - ☐ los dibujos, hojas/figs.
   - ☐ el listado de secuencias *(especificar)*:
   - ☐ cualquier tabla(s) relacionada con el listado de secuencias *(especificar)*:

   ** Si se aplica el punto 4, algunas o todas estas hojas pueden estar marcadas como "reemplazadas."*

Cuadro No. III Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial

1. Los interrogantes en cuanto a si la invención reivindicada parece ser novedosa, implicar una actividad inventiva (no ser obvia), o tener posibilidad de aplicación industrial no se han examinado con respecto a:

   ☐ la solicitud internacional en su totalidad,

   ☒ reivindicaciones, Nos. 20-25

   porque:

   ☐ la aplicación internacional citada, o las reivindicaciones citadas Nos. se refieren al asunto en cuestión que no requiere un examen preliminar internacional *(especificar)*:

   ☐ la descripción, reivindicaciones o dibujos *(indicar elementos particulares más adelante)* o las reivindicaciones citadas Nos. son tan ambiguas que no pudo formarse un concepto significativo *(especificar)*:

   ☐ las reivindicaciones, o las reivindicaciones citadas Nos. están tan inadecuadamente fundamentadas por la descripción que no pudo formarse un concepto significativo.

   ☒ no se ha establecido un reporte de búsqueda internacional para las citadas reivindicaciones Nos. 20-25

   ☐ el listado de secuencia de aminoácidos y/o nucleótidos no cumple la norma contemplada en Anexo C de las Instrucciones Administrativas:

El formato escrito	☐	no se entregó
	☐	no cumple la norma
El formato de lectura por computador	☐	no se entregó
	☐	no cumple la norma

   ☐ las tablas relacionadas con el nucleótido y/o listado de secuencias de aminoácidos, si únicamente en formato de lectura por computador, no cumplen los requerimientos técnicos estipulados en Anexo C-*bis* de las Instrucciones Administrativas.

   ☐ Véase Hoja Separada para más detalles

Cuadro No. V Declaración motivada bajo Artículo 35(2) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración

1. DECLARACIÓN

Novedad (N)	Si:	Reivindicaciones	2-5, 7, 9, 11-17
	No:	Reivindicaciones	1, 6, 8, 10, 18-27, 28
Actividad Inventiva (IS)	Si:	Reivindicaciones	1-17
	No:	Reivindicaciones	1-28
Posibilidad de Aplicación Industrial (IA)	Si:	Reivindicaciones	1-19, 26-28
	No:	Reivindicaciones	

2. Documentos y explicaciones (Regla 70.7)

Véase hoja separada

III Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial

Las reivindicaciones 20-25 se refieren al asunto que esta Oficina considera que está cubierto por las disposiciones de la Regla 67.1 (iv) PCT. En consecuencia, no se formulará dictamen con respecto a la posibilidad de aplicación industrial del asunto de estas reivindicaciones (Artículo 34(4)(a)(I) PCT).

V Declaración motivada en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; citas y explicaciones que sustentan esta declaración

V.1 La presente solicitud se refiere a tiofenos 2-ureido-3-amido-5-fenilo sustituidos y a su uso como inhibidores de cinasa 1 de punto de control.

V.2 Se hace referencia a los siguientes documentos:

D1: WO 03/029241 A
D2: WO 03/028731 A
D3: WO 02/070494 A'

V.3 Novedad

Documento D1 divulga un compuesto de fórmula I, en la cual R^1 es hidrógeno, R^2 es metilo, R^4 es metilo y R^5 es metilo (Ejemplo 28). Más aún, documento D1 divulga tiofenos 2-ureido-3-amido-5-fenilo sustituidos y su uso como inhibidores de cinasa 1 de punto de control (Reivindicación 5).
Documento D1 divulga asimismo el uso de un compuesto de fórmula VI en la manufactura de un compuesto de fórmula I (Esquema II).
Documento D2 divulga tiofenos 2-amido-3-ureido-5-fenilo sustituidos y su uso como inhibidores de cinasa 1 de punto de control (Reivindicación 6).
Documento D3 divulga anillos fenilo sustituidos con $C(O)NR^1R^2$, $N(H)C(O)N(H)R^4$ y OR^5 (véanse, por ejemplo, compuestos 1-6) a usarse como inhibidores de cinasa 1 de punto de control.

Un compuesto de fórmula I para uso como inhibidores de punto de control se divulga en documento D1. Por lo tanto, las reivindicaciones 1, 6, 8,10,18-27 no cumplen los requerimientos de

Artículo 33(2) PCT.

Un compuesto de fórmula I, como se describe en las reivindicaciones 2-5, 7, 9, 11-17 no se divulga en ninguno de los documentos. Por lo tanto, estas reivindicaciones satisfacen los requerimientos de Art. 33(2) PCT.

El uso de un compuesto de fórmula VI para la manufactura de un compuesto de fórmula I se divulga en documento D1. Por lo tanto, la reivindicación 28 no cumple los requerimientos de Art. 33(2) PCT.

V.4 Actividad Inventiva

En vista de que uso de tiofenos 2-ureido-3-amido-5-fenilo sustituidos para la inhibición de cinasa 1 de punto de control es conocido por documento D1, no puede considerarse que la presente solicitud involucre una actividad inventiva (Art. 33(3) PCT).

V.5 Posibilidad de Aplicación Industrial

Para la evaluación de las presentes reivindicaciones 20-25 sobre la cuestión de si tienen posibilidad de aplicación industrial, no existen criterios unificados en los Estados Signatarios del PCT. La patentabilidad puede depender también de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable el asunto de reivindicaciones del uso de un compuesto en tratamiento médico pero puede permitir, no obstante, reivindicaciones de un compuesto conocido para primer uso en tratamiento médico y el uso de tal compuesto para la manufactura de un medicamento para un tratamiento médico nuevo.

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PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	101064-1 WO
I	Title of invention	SUBSTITUTED THIOPHENES AND USES THEREOF
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	AP: (BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH& LI CN CO CR CU CZ DE DK DM DZ EC EE EG 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 MK MN MW MX MZ NA 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 UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address	SE-151 85 Södertälje Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+46 8 553 260 00
II-9	Facsimile No.	+46 8 553 288 20

24 216

III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address	15 Stanhope Gate London Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB
III-2	Applicant and/or Inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ASHWELL, Susan
III-2-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-2-6	State of nationality	GB
III-2-7	State of residence	US
III-3	Applicant and/or Inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	GERO, Thomas
III-3-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or Inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	IOANNIDIS, Stophanos
III-4-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-4-6	State of nationality	GR
III-4-7	State of residence	US

216 217

III-5	Applicant and/or Inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	JANETKA, James
III-5-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
III-6	Applicant and/or Inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	LYNE, Paul
III-6-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-6-6	State of nationality	IE
III-6-7	State of residence	US
III-7	Applicant and/or Inventor	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	OZA, Vibha
III-7-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-7-6	State of nationality	IN
III-7-7	State of residence	US
III-8	Applicant and/or Inventor	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	SPRINGER, Stephanie
III-8-5	Address	37 Village Green Drive North Andover, Massachusetts 01845 United States of America
III-8-6	State of nationality	US
III-8-7	State of residence	US

III-9	Applicant and/or Inventor	
III-9-1	This person is	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	SU, Mei
III-9-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-9-6	State of nationality	CN
III-9-7	State of residence	US
III-10	Applicant and/or Inventor	
III-10-1	This person is	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	YU, Dingwei
III-10-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-10-6	State of nationality	US
III-10-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	GLOBAL INTELLECTUAL PROPERTY
IV-1-2	Address	AstraZeneca AB SE-151 85 Södertälje Sweden
IV-1-3	Telephone No.	+46 8 553 260 00
IV-1-4	Facsimile No.	+46 8 553 288 20
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	

VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	15 August 2003 (15.08.2003)	
VI-1-2	Number	60/495,580	
VI-1-3	Country	US	
VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	28 May 2004 (28.05.2004)	
VI-2-2	Number	60/576,416	
VI-2-3	Country	US	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	79	-
IX-3	Claims	13	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	99	

	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-11	Copy of general power of attorney	reference no. AZAB/FEB04/01	-
IX-11	Copy of general power of attorney	reference no. AZUK/FEB04/01	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	GLOBAL INTELLECTUAL PROPERTY	
X-1-2	Name of signatory	Kevin Bill	
X-1-3	Capacity	Agent	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

101064-1 WO

PCT REQUEST (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared Using		PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)		
0-9	Applicant's or agent's file reference		101064-1 WO		
2	Applicant		ASTRAZENECA AB		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (GBP)	
12-1	Transmittal fee	T	⇨	55	
12-2-1	Search fee	S	⇨	1078	
12-2-2	International search to be carried out by		EP		
12-3	International filing fee (first 30 sheets)	I1	628		
12-4	Remaining sheets		69		
12-5	Additional amount	(X)	7		
12-8	Total additional amount	I2	483		
12-7	I1 + I2 =	I	1111		
12-12	EASY Filing reduction	R	-45		
12-13	Total international filing fee (I-R)	I	⇨	1066	
12-14	Fee for priority document				
	Number of priority documents requested		0		
12-15	Fee per document	(X)	22		
12-16	Total priority document fee:	P	⇨		
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	2199	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions				
	The receiving Office		United Kingdom Patent Office (RO/GB)		
12-20-1	Authorization to charge the total fees indicated above		✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above		✓		
12-20-3	Authorization to charge the fee for priority document		✓		
12-21	Deposit account No.		D02934		
12-22	Date		11 August 2004 (11.08.2004)		
12-23	Name and signature		Helen Dixon		

PCT

Original (for SUBMISSION)

13-2-3	Validation messages Names	Yellow! Agent 1 would not appear to be competent to act before the receiving Office
	Validation messages Names	Green? Applicant 1:Street address missing
	Validation messages Names	Green? Applicant 2:Street address missing
	Validation messages Names	Green? Applicant 9:Street address missing
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
	Validation messages Contents	Green? Priority 2. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: 101064-1 WO
International application No.: PCT/GB2004/003473	International filing date *(day/month/year)*: 12 August 2004 (12.08.2004)	(Earliest) Priority date *(day/month/year)*: 15 August 2003 (15.08.2003)
Title of invention: SUBSTITUTED THIOPHENES AND USES THEREOF		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. / Facsimile No. / Teleprinter No. / Applicant's registration No. with the Office
AstraZeneca AB SE-151 85 Södertälje Sweden	+46 8 553 260 00 +46 8 553 288 20

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SE	SE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1Y 6LN
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ASHWELL, Susan
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	US

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/GB2004/003473

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GERO, Thomas
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

IOANNIDIS, Stephanos
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GR	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

JANETKA, James
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LYNE, Paul
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IE	US

☒ Further applicants are indicated on another continuation sheet.

International application No.
PCT/GB2004/003473

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

OZA, Vibha
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SPRINGER, Stephanie
37 Village Green Drive
North Andover, MA 01845
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SU, Mei
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CN	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

YU, Dingwei
AstraZeneca R&D Boston
35 Gatehouse Drive
Waltham, MA 02451
United States

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/GB2004/003473

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GLOBAL INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).
4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

International application No.
PCT/GB2004/003473

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☒ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in electronic form
7. ☐ tables in electronic form related to a sequence listing
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Macclesfield, 31 May 2005

P. J. French

.....

FRENCH, Philip
Global Intellectual Property, AstraZeneca AB

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

228

Brigard & Castro

BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 20

Firma

Nombre
Cargo

En la Notaría Cuarenta de este círculo, presentó fotocopia que se ha tenido a la vista del original que se ha tenido a la vista

02 FEB. 2004

NOTARIO CUARENTA (E)
Marby Fernando Mejía Sánchez
Bogotá, D.C., Colombia

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domicilied in SE-151 Södertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Macclesfield, Cheshire, England

18th day of July 2003

Signature

Name KEVIN HILL

Title Director, IP Services

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — J B Hodgson
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

   Certified/Attesté

5. at London/à Londres — 6. the/le 17 February 2004

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

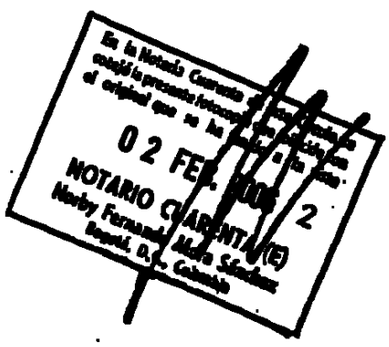
8. Number/sous No — G348987

9. Stamp:
   timbre:

10. Signature: J. Ireland

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.



TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el Poder concedido por **ASTRAZENECA AB**, domiciliada en SE - 151 Sodertalje, Suecia a **Ramiro Castro Duque y/o Juan Pablo Cadena Sarmiento y/o Beatriz Jaramillo S**, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.

AUTENTICACIÓN

(Convención de La Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

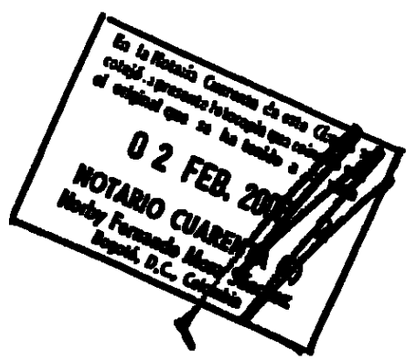
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
   ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

CERTIFICADO

5. en Londres 6. el **17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello 10. Firma

J. Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país.



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GAVIRI-A

REPÚBLICA DE COLOMBIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina:	Registraduría		Notaría	X	Consulado		Corregimiento		Insp. de Policía		Código	9795

País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C. NOTARIA 32.

Datos del fallecido

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción									Hora	Número de certificado de defunción
Año 2004	Mes 10			Día 30					04:10 PM	A- 2094375.

Presunción de muerte

Juzgado que profiere la sentencia	Fecha de la sentencia								
	Año				Mes			Día	

Documento presentado				Nombre y cargo del funcionario
Autorización Judicial		Certificado Médico	X	ANDRES DIAZ CAMPOS. R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO II.

Documentos de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma

Segundo testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma

Fecha de inscripción									Nombre y firma del funcionario que autoriza
Año 2004	Mes 11			Día 02					BLANCA [illegible] ESTUPIÑAN RESTREPO NOTARIA

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO : QUE:

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: ST 62204.....
que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004.....

NOTARIA 32 DEL CIRCULO DE BOGOTA D.C.
SECRETARIO DELEGADO
NELSON FLOREZ C.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1534 DE 1989

253
232

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06022101 00000000 Folios: 232
Fecha (AMD): 2006-03-06 15:14:08
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ( ) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Descripción de la invención.	( )	( )
-Dibujos de ser estos pertinentes.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: 6 Marz / 06

233

PETITORIO

AS: 100.478

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06022101 00000000 Folios: 232
Fecha (AMD): 2006-03-06 16:14:00
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 15-03-2006

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: SE-151 85 Södertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: **JUAN PABLO CADENA SARMIENTO** Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Susan ASHWELL, Thomas GERO, Stophanos IOANNIDIS, James JANETKA, Paul LYNE, Vibha OZA, Stephanie SPRINGER, Mei SU, Dingwei YU **Dirección:** AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); 37 Village Green Drive, North Andover, MA 01845 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451, Estados Unidos de América (Respectivamente) **Nacionalidad o Domicilio:** Estados Unidos de América (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/GB2004/003473 Fecha 12-08-2004
Publicación Internacional No. WO 2005/016909 A1 Fecha 24-02-2005

Título (54): TIOFENOS SUSTITUIDOS Y SUS USOS

7 Clasificación Internacional (51) (C07D333/38,409/12,A61K31/38,A61P35/00 // (C07D409/12,333:00),(C07D409/12,333:00,333:00)(C07D409/12,333:00,241:00)

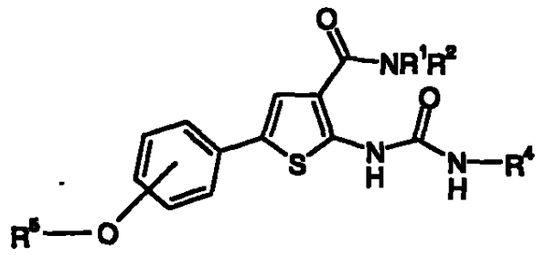
8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	15-08-2003	60/495,580
	US	28-05-2004	60/576,416

9 Comprobante de pago No. 06-4,820 **Fecha** 06-03-2006

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

Reivindicaciones

1. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o precursores hidrolizables *in vivo*:



(I)

en donde:

R^1 y R^2 en cada ocurrencia se seleccionan independientemente de H, opcionalmente sustituido C_{1-6}alquilo, o heterociclilo opcionalmente sustituido; con la condición que R^1 y R^2 no son ambos H; ó R^1 y R^2 y el N, al cual se unen, forman en combinación heterociclilo opcionalmente sustituido;

R^4 se selecciona de H, OH, carbociclilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, o C_{1-6}alquilo opcionalmente sustituido;

R^5 se selecciona de H, carbociclilo opcionalmente sustituido, o C_{1-6}alquilo pcionalmente sustituido.

2. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^2, R^4, y R^5 tienen cualquiera de los significados definidos en la reivindicación 1, y

R^1 es un heterociclilo opcionalmente sustituido.

3. Un compuesto de fórmula (I) o su sal farmacéuticamente aceptable o un precursor hidrolizable *in vivo* como se declara en la reivindicación 1, en donde R^2, R^4, y R^5 tienen cualquiera de los significados definidos en la

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	6 22101
	Solicitud internacional	GB2004/003473
	Fecha inicio fase nacional	15/03/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	5640

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

DORIS ELENA POLO CORDOBA
Jefe de la división de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 26 MAYO 2006
jramos