

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

2020
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Abogado
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Apoderado
Solicitante: PFIZER PRODUCTS INC.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 519 TRASLADOINFORME Folios: 1

ASUNTO	Radicación	03037182
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	12582
	Folios	118

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

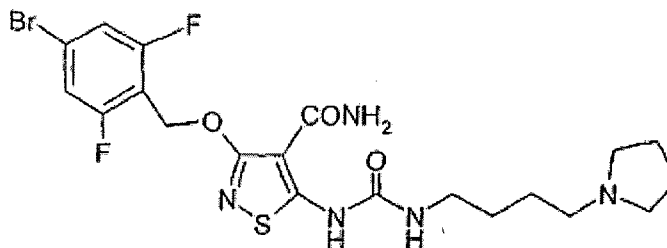
- 1.1. Descripción: Folios: 55 a 80
- 1.2. Reivindicaciones: Folios 81 a 83
- 1.3. Prioridad: fecha: 28/11/2000, país: US, número: 60/253.513

2. Objeto de la invención

- La solicitud hace referencia a: **FORMAS DE SAL DE AMIDA DE ÁCIDO 3-(4-BROMO-2,6-DIFLUORO-BENCILOXI)-5-[3-(4-PIRROLIDIN-1-ILBUTIL) UREIDO] ISOTIAZOL – 4- CARBOXÍLICO Y MÉTODO DE PRODUCCIÓN.**

El objeto de la presente solicitud de patente de invención consiste en:

Formas de sal hidrocioruro, hidrobromuro, hemicitrato, acetato, p-tosilato, L-tartrato, hemisuccinato y mesilato de amida de ácido 3-(4-bromo-2,6-difluorobenciloxi)-5-[3-(4-pirrolidin-1-ilbutil) ureído] isotiazol-4- carboxílico con la siguiente fórmula:



formula I.

Composiciones farmacéuticas que contienen las sales de hidrocloreto, hidrobromuro, hemicitrato, acetato, p-tosilato, L-tartrato, hemisuccinato y mesilato de fórmula I.

Métodos para tratar enfermedades hiperproliferativas, tales como cánceres, en mamíferos, especialmente seres humanos, por administración de las sales anteriores y a los métodos para preparar las formas cristalinas de las sales anteriores.

Reivindicaciones 1 – 14: Reclama protección para sales bromhidrato, hemicitrato, acetato, p-tosilato, L-tartrato, hemisuccinato.

Reivindicación 15-16: Reclama protección para el uso de un compuesto de las reivindicaciones 1, 3, 5, 7, 9, 11 o 13 para la fabricación de un medicamento para el tratamiento de un grupo de patologías.

Reivindicación 17-18: Reclama protección para una composición farmacéutica que comprende un compuesto según las reivindicaciones 1, 3, 5, 7, 9, 11 o 13 para tratar un grupo de patologías.

Reivindicación 19-20: Reclama protección para un método para preparar sales hidrobromuro y hemicitrato que comprende hacer reaccionar ácido cítrico con amida.

El problema planteado en esta solicitud es la necesidad de compuestos útiles en el tratamiento de enfermedades hiperproliferativas, tales como cánceres, en mamíferos, especialmente seres humanos con la ventaja de que proporcionan resultados de dosificación más reproducibles.

Para solucionar este problema técnico la solicitud en estudio proporciona las formas de sal hidrocloreto, hidrobromuro, hemicitrato, acetato, p-tosilato, L-tartrato, hemisuccinato y mesilato de amida de ácido 3-(4-bromo-2,6-difluorobenciloxi)-5-[3-(4-pirrolidin-1-ilbutil)ureido]isotiazol-4-carboxílico, los métodos para producirlas, las composiciones farmacéuticas que las contienen.

- **Clasificación Internacional de Patentes (IPC.)** C07D275/02; A61K31/425; A61K31/427; A61P3/10; A61P9/00; A61P9/10; A61P13/08; A61P13/12; A61P17/00; A61P17/06; A61P19/02; A61P27/02; A61P29/00; A61P35/00; A61P35/02; A61P37/06; C07D275/03; A61K31/425; A61K31/427; A61P3/00; A61P9/00; A61P13/00; A61P17/00; A61P19/00; A61P27/00; A61P29/00; A61P35/00; A61P37/00; C07D275/00

3. De la solicitud de Patente (según el caso)

3.1. Descripción (artículo 28 D. 486)

- Se describen procedimientos para medir la capacidad inhibitoria específica de los compuestos de los cuales no se exponen sus tablas de resultados comparativos contra la anterioridad que evidencie las ventajas descritas

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

- Reivindicaciones 15-16: Se refieren a usos de un compuesto de las reivindicaciones 1, 3, 5, 7, 9, 11 o 13 para la fabricación de un medicamento para el tratamiento de un trastorno hiperproliferativo en un mamífero y su uso en diferentes patologías por lo tanto no se aceptan según la legislación vigente.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 28/11/2000, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Nº	Documento	Título	Fecha de Publicación*
D1	WO 99/62890	ISOTHIAZOLE DERIVATIVES USEFUL AS ANTICANCER AGENTS	9/12/1999

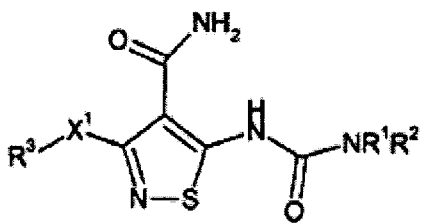
6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

6.1. Nivel inventivo (artículo 18 D486)

- La presente solicitud de patente reivindica (1-20) 7 sales específicas, sus usos, composiciones derivadas de las mismas y métodos de preparación.

Dichas reivindicaciones se ven afectadas por el siguiente documento del Estado de la Técnica más cercano:

D1 que enseña compuestos de fórmula I y sales aceptables farmacéuticamente, prodrogas y solvatos y composiciones que contienen los compuestos mencionados y métodos de tratamiento de desordenes proliferativos en mamíferos administrando dichos compuestos:



- Las sales reivindicadas en la presente solicitud fueron seleccionadas de una lista de sales ya sugeridas en D1 (ver folio 108, líneas 1-12). Realizar esta selección es una forma obvia para llegar al diseño de tales compuestos, por lo tanto no implican una contribución inventiva. Se debe tener en cuenta igualmente que las ventajas *inesperadas* alegadas para las sales reivindicadas no están sustentadas por algún dato experimental, y que además las ventajas similares (ver descripción de la presente aplicación folio 65, líneas 8-27) también deberían sustentarse en el caso de las sales hidrocloreuro y mesilato ya conocidas según D1.
- D1 describe específicamente 3-(4-bromo-2,6-difluoro-benziloxi)-5[3-(4-pirrolidin-1-il-butil)-ureido]-isotiazol-4-amida carboxílico (la base), su sal mesilato y su sal hidrocloreuro, ver reivindicación 9 en sus compuestos 1, 8 y 20 (folio 109, 110), utilizados en el tratamiento de enfermedades proliferativas con las mismas propiedades farmacológicas, (ver reivindicación 10 folio 113).

De esta forma no puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada porque la descripción no presenta datos en tal sentido.

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Por consiguiente, de acuerdo a las consideraciones expuestas anteriormente, resultaría obvio el diseño de este tipo de fármacos para un experto en la materia.

Así las cosas el Problema Técnico Objetivo fundamental de la Invención Reivindicada no puede definirse y los compuestos, métodos y composiciones reivindicados se consideran tan solo una alternativa, sin algún efecto que lo haga superior a **la materia previamente conocida**.

Por lo tanto la materia objeto de las reivindicaciones 1-20 carece de nivel inventivo.

Si el solicitante considera que los compuestos y composiciones de la invención son superiores a los conocidos, este despacho le recomienda aportar datos relacionados para poder llegar a tal conclusión.

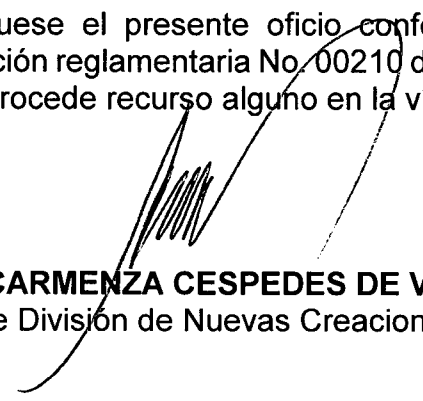
7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO 99/62890	1-20	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 05 OCT. 2007

CONCEPTO TECNICO No. 1665	EXAMINADOR TECNICO Código No. 202087
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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 275/03, 417/12, 487/08, C07C 33/46, 327/58, A61K 31/425 // (C07D 487/08, 209:00, 209:00)		A1	(11) International Publication Number: WO 99/62890 (43) International Publication Date: 9 December 1999 (09.12.99)
(21) International Application Number: PCT/IB99/00797 (22) International Filing Date: 3 May 1999 (03.05.99) (30) Priority Data: 60/087,963 4 June 1998 (04.06.98) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LARSON, Eric, Robert [US/US]; 3 Prospect Street, Mystic, CT 06355 (US). NOE, Mark, Carl [US/US]; 7 Whitehall Lane, Mystic, CT 06355 (US). GANT, Thomas, George [US/US]; 51 Oakwood Road, Niantic, CT 06357 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: ISOTHIAZOLE DERIVATIVES USEFUL AS ANTICANCER AGENTS (1)			
(57) Abstract The present invention relates to compounds of formula (1) and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein X¹, R¹, R² and R³ are as defined herein. The invention also relates to pharmaceutical compositions containing the above compounds and to methods treating hyperproliferative disorders in mammals by administering the above compounds.			

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The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula 1. The compounds of formula 1 that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare

5 pharmaceutically acceptable acid addition salts of such basic compounds of formula 1 are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate,

10 saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula 1 that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the

15 alkali metal or alkaline earth metal salts and particularly, the sodium and potassium salts.

Certain compounds of formula 1 may have asymmetric centers and therefore exist in different enantiomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of formula 1 and mixtures thereof. The compounds of formula 1 may also exist as tautomers. This invention relates to the use of all such tautomers and

20 mixtures thereof.

The subject invention also includes isotopically-labelled compounds, and the pharmaceutically acceptable salts thereof, which are identical to those recited in formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of

25 isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are

30 within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford

35 certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in

with the proviso that said compound of formula 1 is not 1-methyl-3-(4-carbamoyl-3-ethoxy-5-isothiazolyl)urea, 1,1-dimethyl-3-(4-carbamoyl-3-ethoxy-5-isothiazolyl)urea, 1-methyl-3-(4-carbamoyl-3-propoxy-5-isothiazolyl)urea, 1-methyl-3-(4-carbamoyl-3-(methylthio)-5-isothiazolyl)urea, 1-methyl-3-(4-carbamoyl-3-(ethylthio)-5-isothiazolyl)urea, 1,1-dimethyl-3-(4-carbamoyl-3-(ethylthio)-5-isothiazolyl)urea, 1-methyl-3-(4-carbamoyl-3-(propylthio)-5-isothiazolyl)urea, 1,1-dimethyl-3-(4-carbamoyl-3-(propylthio)-5-isothiazolyl)urea, or 1-methyl-3-(4-carbamoyl-3-(isopropylthio)-5-isothiazolyl)urea.

2. A compound according to claim 1 wherein R^2 is H and R^1 is C_1-C_{10} alkyl optionally substituted by 1 or 2 substituents independently selected from $-NR^5R^6$, $-NR^5(CR^6R^7)_tOR^6$ and $-(CH_2)_t(5-10 \text{ membered heterocyclic})$ wherein t is an integer from 0 to 5.

3. A compound according to claim 2 wherein R^1 is selected from propyl, butyl, pentyl and hexyl, and said R^1 groups are optionally substituted by dimethylamino, hydroxy, pyrrolidinyl, morpholino, and ethyl-(2-hydroxy-ethyl)-amino.

4. A compound according to claim 1 wherein R^2 is H and R^1 is $-(CH_2)_t(5-10 \text{ membered heterocyclic})$, wherein t is an integer from 0 to 5; said heterocyclic group is optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; and said R^1 group, including the optionally fused portions of said R^1 group, is optionally substituted by 1 or 2 substituents independently selected from C_1-C_4 alkyl, hydroxy and hydroxymethyl.

5. A compound according to claim 4 wherein the heterocyclic moiety of said R^1 group is selected from morpholino, pyrrolidinyl, imidazolyl, piperazinyl, piperidinyl, and 2,5-diazabicyclo[2.2.1]hept-2-yl, the t variable of said R^1 group ranges from 2 to 5, and said R^1 group is optionally substituted by hydroxy, hydroxymethyl and methyl.

6. A compound according to claim 1 wherein R^3 is $-(CH_2)_t(C_6-C_{10} \text{ aryl})$ wherein t is an integer from 1 to 3 and said R^3 group is optionally substituted by 1 to 4 R^4 groups.

7. A compound according to claim 6 wherein R^3 is benzyl optionally substituted by 1 to 4 substituents independently selected from halo and C_1-C_4 alkyl.

8. A compound according to claim 7 wherein R^3 is benzyl substituted by 1 to 4 substituents independently selected from methyl, fluoro, chloro and bromo.

9. A compound according to claim 1 selected from the group consisting of:

mesylate salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

5-[3-[3-(4-Methyl-piperazin-1-yl)-propyl]-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-[4-[ethyl-(2-hydroxy-ethyl)-amino]-butyl]-ureido]-isothiazole-4-carboxylic acid amide;

- 3-(2-Fluoro-4-methyl-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-
isothiazole-4-carboxylic acid amide;
- 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-(3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-butyl)-
ureido)-isothiazole-4-carboxylic acid amide;
- 5 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-[3-(6-dimethylamino-hexyl)-ureido]-isothiazole-
4-carboxylic acid amide;
- 3-(2-Fluoro-4-methyl-benzyloxy)-5-[3-(5-isopropylamino-pentyl)-ureido]-isothiazole-4-
carboxylic acid amide;
- 10 ~~(hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl)-butyl]-
ureido)-isothiazole-4-carboxylic acid amide;~~
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-
carboxylic acid amide;
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido]-
isothiazole-4-carboxylic acid amide;
- 15 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-[(1-methyl-pyrrolidin-2-yl)-ethyl]-ureido]-
isothiazole-4-carboxylic acid amide;
- 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-
carboxylic acid amide;
- 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-butyl]-
ureido)-isothiazole-4-carboxylic acid amide;
- 20 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(3-hydroxy-5-pyrrolidin-1-yl)-pentyl]-ureido)-
isothiazole-4-carboxylic acid amide;
- 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-[3-[4-(3,4-dihydroxy-pyrrolidin-1-yl)-butyl]-
ureido)-isothiazole-4-carboxylic acid amide;
- 25 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-[4-(3,4-dihydroxy-pyrrolidin-1-yl)-butyl]-
ureido)-isothiazole-4-carboxylic acid amide;
- 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-[3-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-butyl]-
ureido)-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-butyl]-
ureido)-isothiazole-4-carboxylic acid amide;
- 30 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-[3-[4-(3-hydroxy-pyrrolidin-1-yl)-butyl]-ureido)-
isothiazole-4-carboxylic acid amide;
- 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido)-isothiazole-4-
carboxylic acid amide;
- 35 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(4-hydroxy-5-piperidin-1-yl-pentyl)-ureido]-
isothiazole-4-carboxylic acid amide;

- 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-{3-[4-(3-hydroxy-5-piperidin-1-yl-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[4-(2-hydroxymethyl-piperidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;
- 5 3-(2,5-Difluoro-4-methyl-benzyloxy)-5-(3-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(5-hydroxy-6-piperidin-1-yl)-hexyl]-ureido]-isothiazole-4-carboxylic acid amide;
- 3-(4-Bromo-2,3,6-trifluoro-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;
- 10 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl-propyl)-ureido]-isothiazole-4-carboxylic acid amide;
- 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(3-hydroxy-5-pyrrolidin-1-yl-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;
- 15 5-[3-(4-Pyrrolidin-1-yl-butyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;
- 5-[3-(3-Hydroxy-5-pyrrolidin-1-yl-pentyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[3-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;
- 20 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-{3-[3-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-{3-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-ureido}-isothiazole-4-carboxylic acid amide;
- 25 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-{3-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;
- 5-{3-[2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-ureido}-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;
- 30 5-[3-(4-Dimethylamino-butyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;
- 5-[3-(3-Dimethylamino-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;
- 35 5-[3-(3-Hydroxy-5-isopropylamino-pentyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

- 5-[3-(3-Isopropylamino-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-
isothiazole-4-carboxylic acid amide;
- 5-[3-[4-(4-Methyl-piperazin-1-yl)-butyl]-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-
isothiazole-4-carboxylic acid amide;
- 5 5-[3-[4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-butyl]-ureido]-3-(2,3,6-trifluoro-4-methyl-
benzyloxy)-isothiazole-4-carboxylic acid amide;
- 5-[3-(3-Pyrrolidin-1-yl-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-
isothiazole-4-carboxylic acid amide;
- 5-[3-(4-Hydroxy-5-piperidin-1-yl-pentyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-
10 isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(4-imidazol-1-yl-butyl)-ureido]-isothiazole-4-
carboxylic acid amide;
- 5-[3-[4-[Ethyl-(2-hydroxy-ethyl)-amino]-butyl]-ureido]-3-(2,3,6-trifluoro-4-methyl-
benzyloxy)-isothiazole-4-carboxylic acid amide;
- 15 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-[4-(2-hydroxymethyl-piperidin-1-yl)-butyl]-
ureido]-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-(3-hydroxy-5-pyrrolidin-1-yl-pentyl)-ureido]-
isothiazole-4-carboxylic acid amide;
- 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido]-
20 isothiazole-4-carboxylic acid amide;
- 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-ureido]-
isothiazole-4-carboxylic acid amide;
- 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(4-dimethylamino-butyl)-ureido]-isothiazole-
4-carboxylic acid amide;
- 25 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(3-dimethylamino-propyl)-ureido]-isothiazole-
4-carboxylic acid amide;
- 3-(4-Bromo-2,3,6-trifluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-
4-carboxylic acid amide;
- 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-(4-imidazol-1-yl-butyl)-ureido]-isothiazole-
30 4-carboxylic acid amide;
- 3-(4-Chloro-2,3,6-difluoro-benzyloxy)-5-[3-[3-[ethyl-(2-hydroxy-ethyl)-amino]-propyl]-
ureido]-isothiazole-4-carboxylic acid amide;
- 3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-[3-[ethyl-(2-hydroxy-ethyl)-amino]-propyl]-
ureido]-isothiazole-4-carboxylic acid amide;
- 35 5-[3-(3-Methylamino-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-
4-carboxylic acid amide;

5-[3-(3-Amino-propyl)-3-methyl-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(4-Diethylamino-butyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5 3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(3-pyrrolidin-1-yl-propyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(3-Chloro-2,6-difluoro-4-methyl-benzyloxy)-5-[3-(4-dimethylamino-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

10 5-[3-(4-[Bis-(2-hydroxy-ethyl)-amino]-butyl)-ureido]-3-(2,6-difluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

and the pharmaceutically acceptable salts, prodrugs and solvates of said compounds.

10. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

15 11. The pharmaceutical composition of claim 10 wherein said hyperproliferative disorder is a cancer selected from brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, oesophageal, gynecological and thyroid cancer.

20 12. The pharmaceutical composition of claim 10 wherein said disorder is a non-cancerous hyperproliferative disorder

13. The pharmaceutical composition of claim 12 wherein said disorder is a benign hyperplasia of the skin or prostate.

25 14. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound according to claim 1.

15. The method of claim 14 wherein said method is for the treatment of a cancer selected from brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.

30 16. The method of claim 14 wherein said method is for the treatment of a non-cancerous hyperproliferative disorder.

17. The method of claim 16 wherein said method is for the treatment of a benign hyperplasia of the skin or prostate.

35 18. A method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound according to claim 1 in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor