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(54) Title: USE OF C-KIT INHIBITORS FOR TREATING HIV RELATED DISEASES

(57) Abstract: The present invention relates to a method for treating HIV related diseases comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cell degranulation, to a human in need of such treatment. Such compounds can be chosen from c-kit inhibitors and more particularly non-toxic, selective and potent c-kit inhibitors. Preferably, said inhibitors are unable to promote death of IL-3 dependent cells cultured in presence of IL-3.



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Use of c-kit inhibitors for treating HIV related diseases

5 The present invention relates to a method for treating HIV related diseases comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cell degranulation, to a human in need of such treatment. Such compounds can be chosen from c-kit inhibitors and more particularly non-toxic, selective and potent c-kit inhibitors. Preferably, said inhibitor is unable to promote death of IL-3 dependent cells
10 cultured in presence of IL-3.

AIDS was reported in the early eighties as resulting from progressive human immunodeficiency virus (HIV) infection. In infected subjects, HIV progressively destroys or damages cells of the body's immune system. Gradually, immune responses to
15 diseases and pathogens infection deteriorate. As of today, it is estimated that more than 900,000 Americans may be infected with HIV.

Approved drugs for treating HIV infection include nucleoside reverse transcriptase (RT) inhibitors, such as AZT, ddC, ddI, d4T, and 3TC. The aim of these nucleotide analogs is
20 to slow the spread of HIV in the body and delay the onset of opportunistic infections. More recently, protease inhibitors have been approved for blocking virus cycles at a later step. In addition, combination treatment using both drugs is necessary to avoid HIV become resistant. However, these treatments do not represent a cure and severe side effects are commonly observed.

25

Furthermore, these medications are active when the virus is replicating but are inefficient while the virus is dormant. A report in the Journal of Virology (2000;74:7824-7833)

reveals that latent HIV reservoirs form when the virus infects activated T cells and when these cells enter a resting state. For example, the half-life of replication-competent HIV in the pool of latently infected resting CD4⁺ T cells has been estimated to be about 44 months. There are other CD34⁺ cells that may serve as a reservoir for HIV. Among these
5 cells, it was found that mast cell progenitors can be infected and can retain the virus in vitro (Bannert et al, Journal of Virology, November 2001, p. 10808-10814, Vol. 75, No. 22). Furthermore, Marone reported that there is evidence that human Fc epsilon RI(+) cells could be infected in vitro by M-tropic HIV-1 strains. (Marone G, de Paulis A, Florio G, Petraroli A, Rossi FW, Triggiani M. Int Arch Allergy Immunol. 2001
10 Jun;125(2):89-95). There is only few data available concerning the role of mast cells in defence against viral pathogens, however, mast cells have been demonstrated to be a potential reservoir of infection for several pathogens, such as HIV-1 and dengue, and capable of producing mediators following challenge with a number of viral products. (Marshall JS, King CA, McCurdy JD. Mast cell cytokine and chemokine responses to
15 bacterial and viral infection. Curr Pharm Des. 2003;9(1):11-24).

Mast cells (MC) are tissue elements derived from a particular subset of hematopoietic stem cells that express CD34, c-kit and CD13 antigens (Kirshenbaum, 1999 and Ishizaka, 1993). Immature MC progenitors circulate in the bloodstream and differentiate
20 in tissues. These differentiation and proliferation processes are under the influence of cytokines, one of utmost importance being Stem Cell Factor (SCF), also termed Kit ligand (KL), Steel factor (SL) or Mast Cell Growth Factor (MCGF). SCF receptor is encoded by the proto-oncogene c-kit, that belongs to type III receptor tyrosine kinase subfamily (Boissan, 2000). This receptor is also expressed on others hematopoietic or
25 non hematopoietic cells. Mast cells are characterized by their heterogeneity, not only regarding tissue location and structure but also at the functional and histochemical levels (Aldenberg, 1994 ; Bradding, 1995 ; Irani, 1991 , 1989 and Welle, 1997). Li and al, demonstrated that many patients with acquired immunodeficiency syndrome have HIV-

1-infected MCs/basophils in their peripheral blood using a population of metachromatic cells with mast cell (MC) and basophil features. These metachromatic cells express on their surface the high-affinity IgE receptor (FcεRI), CD4, and the chemokine receptors CCR3, CCR5, and CXCR4, but not the T-cell surface protein CD3 and the monocyte/macrophage surface protein CD68. This lead to susceptibility of mast cells (MCs)/basophils to revirus. (Li Y, Li L, Wadley R, Reddel SW, Qi JC, Archis C, Collins A, Clark E, Cooley M, Kouts S, Naif HM, Alali M, Cunningham A, Wong GW, Stevens RL, Krilis SA. Mast cells/basophils in the peripheral blood of allergic individuals who are HIV-1 susceptible due to their surface expression of CD4 and the chemokine receptors CCR3, CCR5, and CXCR4. *Blood*. 2001 Jun 1;97(11):3484-90.) Qi and al confirmed that AIDS patients often contain HIV-1-infected mast cells (MCs)/basophils in their peripheral blood. (Qi JC, Stevens RL, Wadley R, Collins A, Cooley M, Naif HM, Nasr N, Cunningham A, Katsoulotos G, Wanigasek Y, Roufogalis B, Krilis SA. IL-16 regulation of human mast cells/basophils and their susceptibility to HIV-1. *J Immunol*. 2002 Apr 15;168(8):4127-34).

When infected in vitro with viruses pseudotyped with different HIV and simian immunodeficiency virus envelope glycoproteins, only M-tropic and dualtropic, but not T-tropic, viruses were able to enter mast cell progenitors. Cultures infected with replication-competent virus produced progressively increasing amounts of virus for 21 days as indicated by p24 antigen detection. Mast cell progenitors that were exposed to an M-tropic, green fluorescent protein-expressing HIV-1 strain exhibited fluorescence indicative of viral entry and replication on a single-cell level and retained virus production during differentiation. We postulate here that mast cells may play a larger role in HIV infection than previously thought. Indeed, mast cells can contain and continue to produce large amounts of an HIV-like virus even after the virus depletes CD4+T cells. This discovery provides an explanation on how the virus might survive despite the use

of reverse transcriptase and protease inhibitors. Moreover, we have observed that MC has a long life and can migrate throughout the body.

As a consequence, we propose to deplete mast cells to eradicate latent HIV virus in the course of reverse transcriptase and protease inhibitors therapy. In connection with the present invention, we have discovered that c-kit inhibitors are particularly suited for depleting HIV infected mast cells and could be a new route for treating HIV infection and related diseases as well as delaying the onset of AIDS through inhibition of mast cells.

10

Description

The present invention relates to a method for treating HIV infection and related diseases, including human immunodeficiency virus type 1 and 2, or delaying the onset of acquired immunodeficiency syndrome (AIDS), comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cells degranulation in a human in need of such treatment.

Said method for treating HIV infection and related diseases or delaying the onset of AIDS can comprise administering a c-kit inhibitor to a human in need of such treatment.

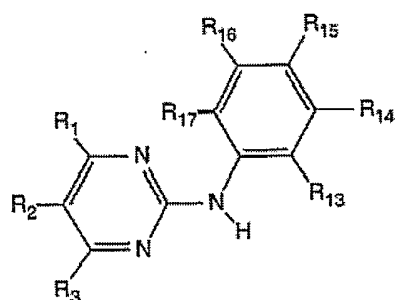
Preferred compounds are c-kit inhibitor, more particularly a non-toxic, selective and potent c-kit inhibitor. Such inhibitors can be selected from the group consisting of 2-(3-Substitutedaryl)amino-4-aryl-thiazoles such as 2-(3-amino)arylamino-4-aryl-thiazoles, 2-aminoaryloxazoles, pyrimidine derivatives, pyrrolopyrimidine derivatives, quinazoline derivatives, quinoxaline derivatives, pyrazoles derivatives, bis monocyclic, bicyclic or heterocyclic aryl compounds, vinylene-azaindole derivatives and pyridyl-quinolones

derivatives, styryl compounds, styryl-substituted pyridyl compounds, seleoindoles, selenides, tricyclic polyhydroxylic compounds and benzylphosphonic acid compounds.

Among preferred compounds, it is of interest to focus on pyrimidine derivatives such as
 5 N-phenyl-2-pyrimidine-amine derivatives (US 5,521,184 and WO 99/03854), indolinone derivatives and pyrrol-substituted indolinones (US 5,792,783, EP 934 931, US 5,834,504), US 5,883,116, US 5,883,113, US 5, 886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, US 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520
 10 722, US 3,772,295 and US 4,343,940), 4-amino-substituted quinazolines (US 3,470,182), 4-thienyl-2-(1H)-quinazolones, 6,7-dialkoxyquinazolines (US 3,800,039), aryl and heteroaryl quinazoline (US 5,721,237, US 5,714,493, US 5,710,158 and WO 95/15758), 4-anilinoquinazoline compounds (US 4,464,375), and 4-thienyl-2-(1H)-quinazolones (US 3,551,427).

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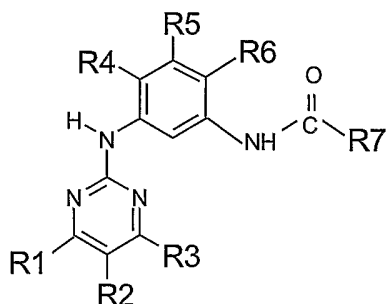
So, preferably, the invention relates to a method for treating HIV related diseases and related disorders comprising administering a non toxic, potent and selective c-kit inhibitor is a pyrimidine derivatives, more particularly N-phenyl-2-pyrimidine-amine derivatives of formula I :



20

wherein the R1, R2, R3, R13 to R17 groups have the meanings depicted in EP 564 409 B1, incorporated herein in the description.

Preferably, the N-phenyl-2-pyrimidine-amine derivative is selected from the compounds corresponding to formula II :



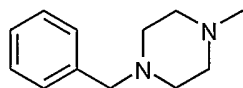
5

Wherein R1, R2 and R3 are independently chosen from H, F, Cl, Br, I, a C1-C5 alkyl or a cyclic or heterocyclic group, especially a pyridyl group;

R4, R5 and R6 are independently chosen from H, F, Cl, Br, I, a C1-C5 alkyl, especially a methyl group;

10 and R7 is a phenyl group bearing at least one substituent, which in turn possesses at least one basic site, such as an amino function.

Preferably, R7 is the following group :



15 Among these compounds, the preferred are defined as follows :

R1 is a heterocyclic group, especially a pyridyl group,

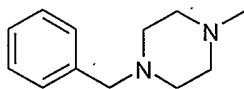
R2 and R3 are H,

R4 is a C1-C3 alkyl, especially a methyl group,

R5 and R6 are H,

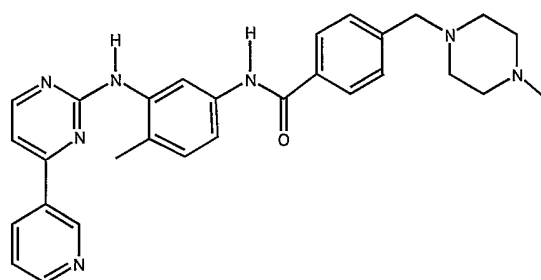
20 and R7 is a phenyl group bearing at least one substituent, which in turn possesses at least one

basic site, such as an amino function, for example the group :



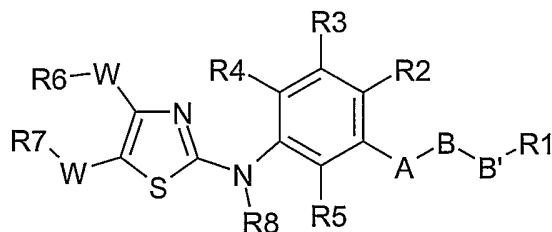
Therefore, in a preferred embodiment, the invention relates to a method for treating HIV related disorders comprising the administration of an effective amount of the compound known in the art as CGP57148B :

4-(4-méthylpipérazine-1-ylméthyl)-N-[4-méthyl-3-(4-pyridine-3-yl)pyrimidine-2-ylamino]phényl]-benzamide corresponding to the following formula :



The preparation of this compound is described in example 21 of EP 564 409 and the β -form, which is particularly useful is described in WO 99/03854.

In another preferred embodiment, the invention contemplates the method mentioned above, wherein said c-kit inhibitor is selected from **2-(3-Substitutedaryl)amino-4-aryl-thiazoles** such as those for which the applicant filed PCT/IB2005/000401, incorporated herein by reference, especially compounds of **formula III** :



FORMULA III

wherein

R⁶ and R⁷ are independently from each other chosen from one of the following:

- i) hydrogen, a halogen (selected from F, Cl, Br or I),
- 5 ii) an **alkyl¹** group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms, or from 2 or 3 to 10 carbon atoms, (for example methyl, ethyl, propyl, butyl, pentyl, hexyl...) and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl,
10 cyano, nitro, formyl;
- (iii) an **aryl¹** group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as
 - halogen(selected from I, F, Cl or Br);
 - an **alkyl¹** group;
 - 15 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
 - trifluoromethyl, O-**alkyl¹**, carboxyl, cyano, nitro, formyl, hydroxy, NH-**alkyl¹**, N(**alkyl¹**)(**alkyl¹**), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- 20 (iv) a **heteroaryl¹** group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as
 - halogen (selected from F, Cl, Br or I);
 - 25 - an **alkyl¹** group;
 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,

- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;

(v) trifluoromethyl, carboxyl, cyano, nitro, formyl, hydroxy, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality.

R⁸ is one of the following:

- (i) hydrogen, or
- 10 (ii) a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
- (iii) CO-R8 or COOR8 or CONHR8 or SO2R8 wherein R8 may be
- 15 - a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
- an aryl group such as phenyl or a substituted variant thereof bearing any
- 20 combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro,
- 25 formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a pendant basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at

least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
- a heteroaryl group such as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

R₂, R₃, R₄ and R₅ each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

A is : CH₂, O, S, SO₂, CO, or COO,

B is a bond or NH, NCH₃, NR*, (CH₂)_n (n is 0, 1 or 2), O, S, SO₂, CO, or COO,

B' is a bond or NH, NCH₃, NR*, (CH₂)_n (n is 0, 1 or 2), O, S, SO₂, CO or COO;

R* being an alkyl¹, aryl¹ or heteroaryl¹

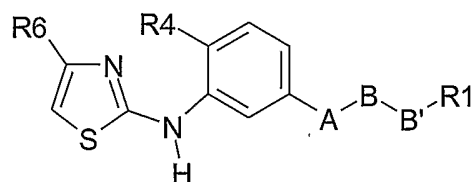
- 5 **W** is a bond or a linker selected from NH, NHCO, NHCOO, NHCONH, NHSO₂, NHSO₂NH, CO, CONH, COO, COCH₂, (CH₂)_n (n is 0, 1 or 2), CH₂-CO, CH₂COO, CH₂-NH, O, OCH₂, S, SO₂, and SO₂NH

R¹ is :

- 10 a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing
- 15 a pendant basic nitrogen functionality
- c) an alkyl¹, aryl¹ or heteroaryl¹.

It will be understood that a C1-C10 alkyl encompasses a methyl, ethyl, propyl, and a C2
20 to C4 alkyl or a C2 to C10 alkyl.

For example, a subset of compounds may correspond to



Wherein R₁, R₄ and R₆ have the meaning as defined above.

25

It will be understood that A-B-B' includes but is not limited to :

CH₂, CH₂-CO, CH₂-CO-CH₂, CH₂COO, CH₂-CH₂-CO, CH₂-CH₂-COO, CH₂-NH, CH₂-CH₂-NH, CH₂-NH-CH₂ or CH₂-NH-CO or CH₂-CO-NH

It will be understood that A-B-B' also includes but is not limited to :

CO-CH₂, COO-CH₂, CO-CH₂-CH₂, CO-NH, or CO-NH-CH₂

5 as well as O-CH₂

It will also be understood that NH in B or B' can also be NCH₃

In the above formula III, when W is other than a single bond, it will be understood that
10 A can be also be NH or NCH₃.

In the above formula, the following combinations are contemplated :

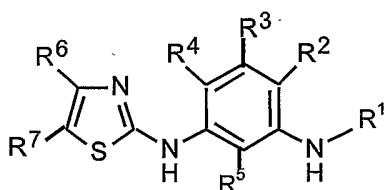
- R₆ is (iv), R₄ is H or CH₃, A-B-B' is CO-NH and R₁ is as defined above.
- R₆ is (iv), R₄ is H or CH₃, A-B-B' is CH₂-CO-NH and R₁ is as defined above.
- 15 - R₆ is (iv), R₄ is H or CH₃, A-B-B' is CH₂-CO and R₁ is as defined above.
- R₆ is (iv), R₄ is H or CH₃, A-B-B' is CH₂-NH-CO and R₁ is as defined above.
- R₆ is (iv), R₄ is H or CH₃, A-B-B' is CH₂-NH and R₁ is as defined above.
- R₆ is (iv), R₄ is H or CH₃, A-B-B' is CH₂ and R₁ is as defined above.
- R₆ is W-(iv), R₄ is a C₁-C₂ alkyl, A-B-B' is CO-NH and R₁ is as defined above.
- 20 - R₆ is (iv), R₄ is a C₁-C₂ alkyl, A-B-B' is CH₂-CO-NH and R₁ is as defined above.
- R₆ is (iv), R₄ is a C₁-C₂ alkyl, A-B-B' is CH₂-CO and R₁ is as defined above.
- R₆ is a pyridyl according to (iv), R₄ is a C₁-C₂ alkyl, A-B-B' is CO-NH, CH₂-CO-NH, CH₂-CO, CH₂-NH, CH₂-NH-CO and R₁ is as defined above.

25 In the above combination, R₁ can be an alkyl¹.

In the above combination, R₁ can be an aryl¹.

In the above combination, R₁ can be an heteroaryl¹.

In another preferred embodiment, the invention contemplated the method mentioned above, wherein said c-kit inhibitor is selected from 2-(3-amino)arylamino-4-aryl-thiazoles such as those for which the applicant filed WO 2004/014903, incorporated herein in the description, especially compounds of formula IV :



5

FORMULA IV

and wherein R¹ is :

- a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
- c) a -CO-NH-R, -CO-R, -CO-OR or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

R² is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R³ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁴ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁵ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁶ is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination,
5 at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- 10 (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,
- iv) H, a halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear
15 or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

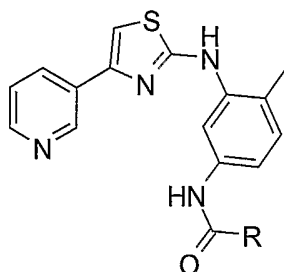
and R⁷ is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination,
20 at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- 25 (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

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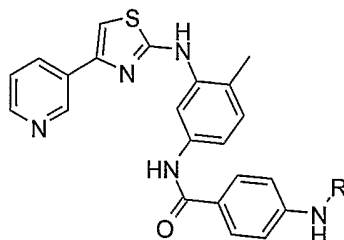
In another preferred embodiment, when R¹ has the meaning depicted in c) above, the invention is directed to compounds of the following formulas:

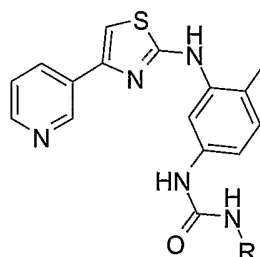
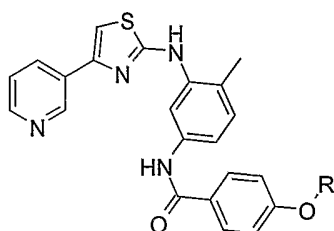
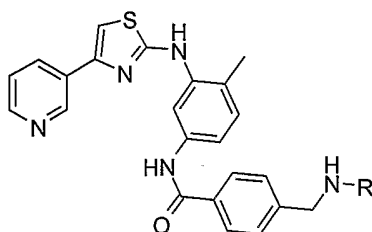


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality.

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Among the particular compounds in which R¹ has the meaning as depicted in c) above, the invention is directed to **amide-aniline**, **amide-benzylamine**, **amide-phenol**, **urea** compounds of the following formulas respectively :

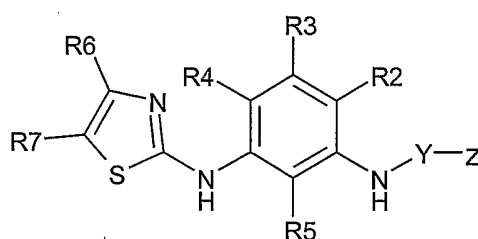




wherein R is H or an organic group that can be selected for example from a linear or
 5 branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at
 least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an
 aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen
 selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or a
 a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl
 10 or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected
 from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality;
 a -SO₂-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally
 substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and / or
 bearing a pendant basic nitrogen functionality; or a -CO-R or a -CO-NRR' group,
 15 wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or

heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in a) and b) above, the invention is directed to N-Aminoalkyl-N'-thiazol-2-yl-benzene-1,3-diamine compounds of the following **formula IVbis**:



wherein Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms;

wherein Z represents an aryl or heteroaryl group, optionally substituted at one or more ring position with any permutation of the following groups:

- a halogen such as F, Cl, Br, I;
- a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- an O-R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one

heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an NRaRb, where Ra and Rb represents a hydrogen, or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality or a cycle; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally

25 - a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally

- substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- 5
- an NHCOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one
 - 10 heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
 - 15 - an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one
 - 20 heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
 - 25 - an NHCONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br

- and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- 5 - an OSO_2R , where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- 10 - an NRaOSO_2Rb , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- 15 - an NRaOSO_2Rb , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- 20 - an NRaOSO_2Rb , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- 25 R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁴ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁵ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

5 R⁶ is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

10 (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from
15 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

20 and R⁷ is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

25 (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

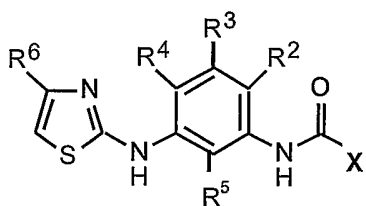
(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any

combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

- iv) H, an halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.
- It will be understood that a C1-C10 alkyl encompasses a methyl, ethyl, propyl, and a C2 to C4 alkyl or a C2 to C10 alkyl.

- 10 An example of preferred compounds of the above formula is depicted below:
4- {[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester

- Among the compounds of formula III or IV, the invention is particularly embodied by
15 the compounds of the following formula V:

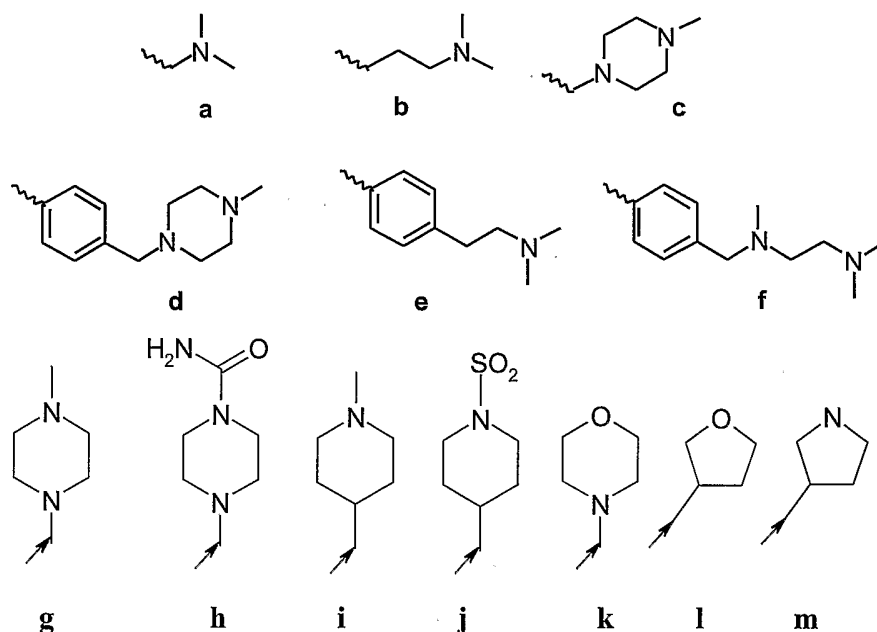


FORMULA V

- wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, a heteroaryl, an alkyl, or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, a heteroaryl, an alkyl or a cycloalkyl group substituted with an aryl, a heteroaryl, an alkyl or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen

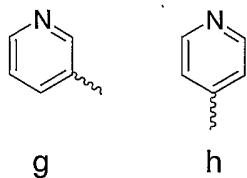
- chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,
- R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- 5 R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10
10 carbon atoms, trifluoromethyl or alkoxy;
- R^6 is one of the following:
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
 - 15 (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
 - (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any
20 combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
 - iv) H, a halogen selected from I, F, Cl or Br; NH_2 , NO_2 or SO_2-R , wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl,
25 Br and F, and / or bearing a pendant basic nitrogen functionality.
- In another alternative, substituent R_6 , which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

Among the preferred compounds corresponding formula III, IV or V, the invention is directed to compounds in which R¹ or X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures a to f and g to m shown below, wherein the wavy line corresponds to the point of attachment to core structure of formula III, IV or V:

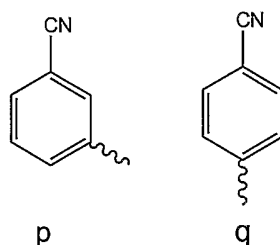


Among group a to f, is preferentially group d. Also, for g to m, the arrow may include a point of attachment to the core structure via a phenyl group.

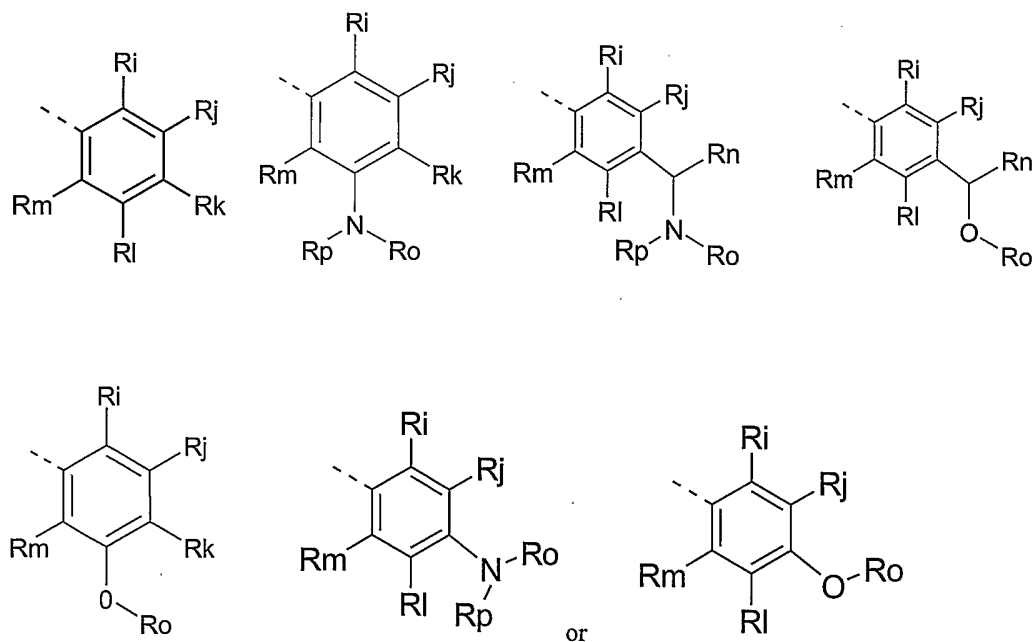
Furthermore, among the preferred compounds of formula III, IV or V, the invention concerns the compounds in which R² and R³ are hydrogen. Preferentially, R⁴ is a methyl group and R⁵ is H. In addition, R⁶ is preferentially a 3-pyridyl group (cf. structure g below), or a 4-pyridyl group (cf. structure h below) or a benzonitrile group. The wavy line in structure g and h correspond to the point of attachment to the core structure of formula III, IV or V.



Alternatively, among the preferred compounds of formula **III**, **IV** or **V**, the invention concerns the compounds in which R6 or R7 is preferentially a cyanophenyl group as shown below, wherein the wavy line in structure p and q correspond to the point of attachment to the core structure of formula **III**, **IV** or **V**:



In one particular embodiment, **R1** in formula **III** and **IV**, **X** in formula **V** and **Z** in formula **IVbis** can be :



wherein **Ri, Rj, Rk, Rl, Rm, Ro, and Rp** are independently chosen from :

- H, an halogen such as Cl, F, Br, I ; a trifluoromethyl group, a CN group, SO₂, OH, or a group selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
- a NRR', NRCOR, NRCONR'R", NROSO₂R', SO₂-R, COOR, CONRR', NHCOOR, CO-R, CO-NRR', OR or OSO₂R group where R and R' are idenpendently chosen from H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

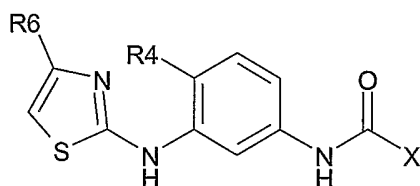
For example, one of Ri, Rj, Rk, Rl, Rm, Ro or Rp is selected from group a, b, c, g, h, i, j, k, l, m as defined above such as Rk is one of a, b, c, g, h, i, j, k, l, m and Ri, Rj, Rl, Rm is H.

Thus, the invention contemplates:

- 1- A compound of formula V as depicted above, wherein X is group d and R⁶ is a 3-pyridyl group.

- 2- A compound of formula V as depicted above, wherein X is group **d** and R⁴ is a methyl group.
- 3- A compound of formula III or IV as depicted above, wherein R¹ is group **d** and R² and/or R³ and/or R⁵ is H.
- 5 4- A compound of formula III or IV as depicted above, wherein R⁶ is a 3-pyridyl group and R⁴ is a methyl group.
- 5- A compound of formula III or IV as depicted above, wherein R² and/or R³ and/or R⁵ is H and R⁴ is a methyl group.
- 6- A compound of formula III or IV as depicted above wherein R² and/or R³ and/or R⁵ is H, R⁴ is a methyl group and R⁶ is a 3-pyridyl group.
- 10

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein R₂, R₃, R₅ are hydrogen, corresponding to the following formula



- 15 wherein X is R or NRR' and wherein R and R' are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
- 20 a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
- a -SO₂-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing
- 25

a pendant basic nitrogen functionality; or a -CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

5 R⁴ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁶ is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups
10 containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any
15 combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and
20 optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

In another alternative, substituent R₆, which in the formula III is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

25

Examples :

2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole

4-(4-Methyl-piperazin-1-ylmethyl)-N-[3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

- N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- 5 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrazin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 2-[5-(3-Iodo-benzoylamino)-2-methyl-phenylamino]-thiazole-4-carboxylic acid ethyl ester
- 2-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-benzoylamino]-phenylamino}-thiazole-4-carboxylic acid ethyl ester
- 10 2-(2-chloro-5-amino)phenyl-4-(3-pyridyl)-thiazole
- 3-Bromo-N-{3-[4-(4-chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-benzamide
- {3-[4-(4-Chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-carbamic acid isobutyl ester
- 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-
- 15 carboxylic acid ethyl ester
- 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid (2-dimethylamino-ethyl)-amide
- N-{3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- 20 4-(4-Methyl-piperazin-1-ylmethyl)-N-{4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl}-benzamide
- N-{4-Methyl-3-[4-(3-nitro-phenyl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- N-{3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-
- 25 ylmethyl)-benzamide
- N-{3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- N-{3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- 30 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide

2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide

3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide

5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester

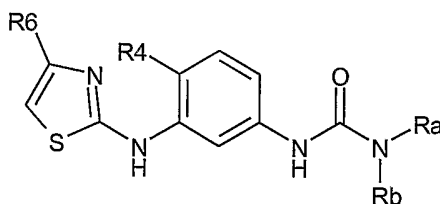
5 1-Methyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide

4-tert-Butyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-yl-butyramide

10

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein X is a urea group, a -CO-NRR' group, corresponding to the [3-(thiazol-2-ylamino)-phenyl]-urea family and the following formula:



15 wherein Ra, Rb are independently chosen from Y-Z as defined above or

H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

25 a -SO₂-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a -CO-R or a -CO-NRR' group,

wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

R⁴ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁶ is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- 10 (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 15 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, 20 Br and F, and / or bearing a pendant basic nitrogen functionality.

Example 1

- 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 25 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea
- 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea
- 4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester
- 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea

- 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 5 1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 10 1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
- 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea
- 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 15 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 20 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]carbamoyl}-phenyl)-ureido)-benzoic acid ethyl ester
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide
- 4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 25 4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide
- 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 30

- 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 5 Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester
- 4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(thiophene-2-sulfonylamino)-benzamide
- 10 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide
- 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 15 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide
- Benzo[1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide
- 20 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-4-pyridin-4-yl-benzamide
- 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
- 25 3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester
- 4-Aminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester
- 30 3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide

- 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide
- 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide
- 5 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide
- 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 10 4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 15 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

Example 2

- 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 20 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide
- 25 4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide
- 4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid
- 30 tert-butyl ester

- 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-3-trifluoromethyl-benzamide
- 5 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- N-{3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- 10 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide
- 15 N-{3-[4-(4-Cyano-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- 4-[1-(4-Methyl-piperazin-1-yl)-ethyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide
- 20 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide
- N-{4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide
- 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide
- 25 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide
- 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[(3-morpholin-4-yl-propylamino)-methyl]-benzamide
- 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide
- 30

4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide

N-{3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

- 5 N-{3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamides

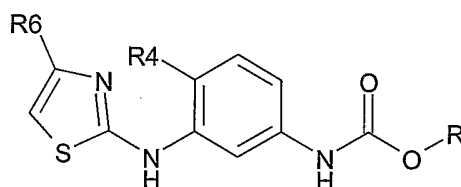
Example 3

3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

- 10 3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-morpholin-4-yl-benzamide

- Among the compounds of formula IV, the invention is particularly embodied by the
15 compounds wherein X is a -OR group, corresponding to the family [3-(Thiazol-2-ylamino)-phenyl]-carbamate and the following formula IV-6



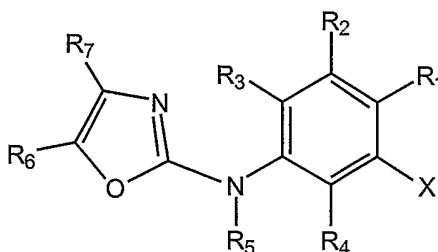
FORMULA IV-6

- 20 wherein R is independently chosen from an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a
25 pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally

substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality;

R4 and R6 are as defined above.

- 5 In still another preferred embodiment, the invention contemplated the method mentioned above, wherein said c-kit inhibitor is selected from **2-aminoaryloxazoles of formula X** :



10

FORMULA X

wherein substituents R1 - R7 and X are defined as follows:

- R1, R2, R3 and R4 each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

R5 is one of the following:

(i) hydrogen, or

(ii) a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or

(iii) CO-R8 or COOR8 or CONHR8 or SO2R8 wherein R8 may be

- a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or

- an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a pendant basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or

- a heteroaryl group such as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and

optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

10

R6 and R7 each independently are selected from:

- i) hydrogen, a halogen (selected from F, Cl, Br or I), or
 - ii) an **alkyl**¹ group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl, cyano, nitro, formyl; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality ; as well as a cycloalkyl or aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality, or
 - (iii) an **aryl**¹ group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as
- halogen(selected from I, F, Cl or Br);
 - an **alkyl**¹ group;
 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;

25

- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
 - NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or
5 CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl, or
- (iv) a **heteroaryl¹** group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinoliny group, which may additionally bear any
10 combination, at any one ring position, of one or more substituents such as
- halogen (selected from F, Cl, Br or I);
 - an alkyl¹ group;
 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
 - 15 - trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
 - NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds
20 to hydrogen, alkyl¹, or
- (v) an O-aryl¹, or NH-aryl¹, or O-heteroaryl¹ or NH-heteroaryl¹ group
- (vi) trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality, or
- 25 (vi) NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl.

X is:

-NR₉R₁₀, wherein R₉ and / or R₁₀ are hydrogen or:

i) an alkyl¹ group, CF₃ or

ii) an aryl¹, heteroaryl¹ or cycloalkyl group optionally substituted by a pendant basic nitrogen functionality, or

iii) a CO-R, COO-R, CON-RR' or SO₂-R, where R and R' are a hydrogen, alkyl¹, aryl¹ or heteroaryl¹, optionally substituted by a pendant basic nitrogen functionality;

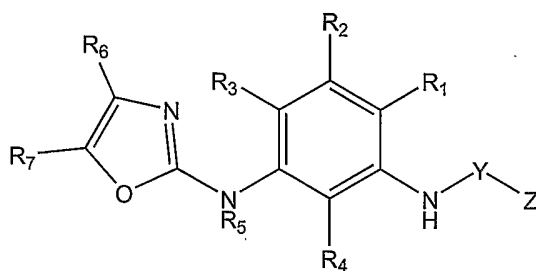
or:

-CO-NR₉R₁₀, wherein R₉ and / or R₁₀ are hydrogen or:

i) an alkyl¹ group, CF₃ or

ii) an aryl¹, heteroaryl¹ or cycloalkyl group optionally substituted by a pendant basic nitrogen functionality.

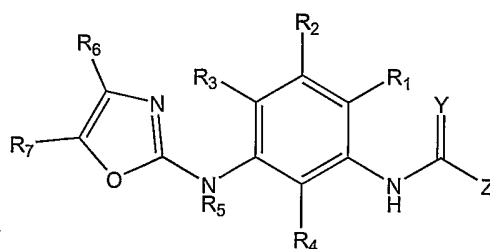
Such compound may be selected from N-Aminoalkyl-N'-oxazol-2-yl-benzene-1,3-diamines of the following formula:



wherein R₅ = H, Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms and Z represents an aryl or a heteroaryl group, optionally substituted by a pendant basic nitrogen functionality.

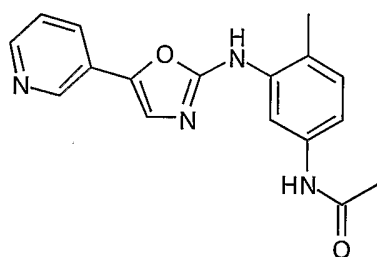
For example, it is the 4-{[4-Methyl-3-(4-pyridin-3-yl-oxazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester.

The above 2-aminoaryloxazoles compounds may have the formula XI:



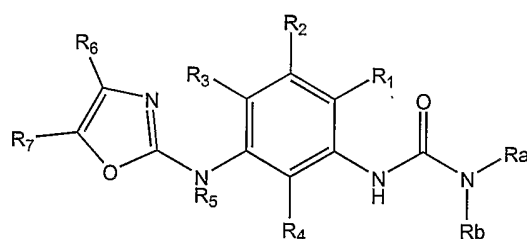
FORMULA XI

- 5 Wherein R₅ is H, Y is selected from O, S and Z corresponds to H, alkyl, or NRR', wherein R and R' are independently chosen from H or alkyl¹ or aryl¹ or heteroaryl¹, optionally substituted by a pendant basic nitrogen functionality, for example :



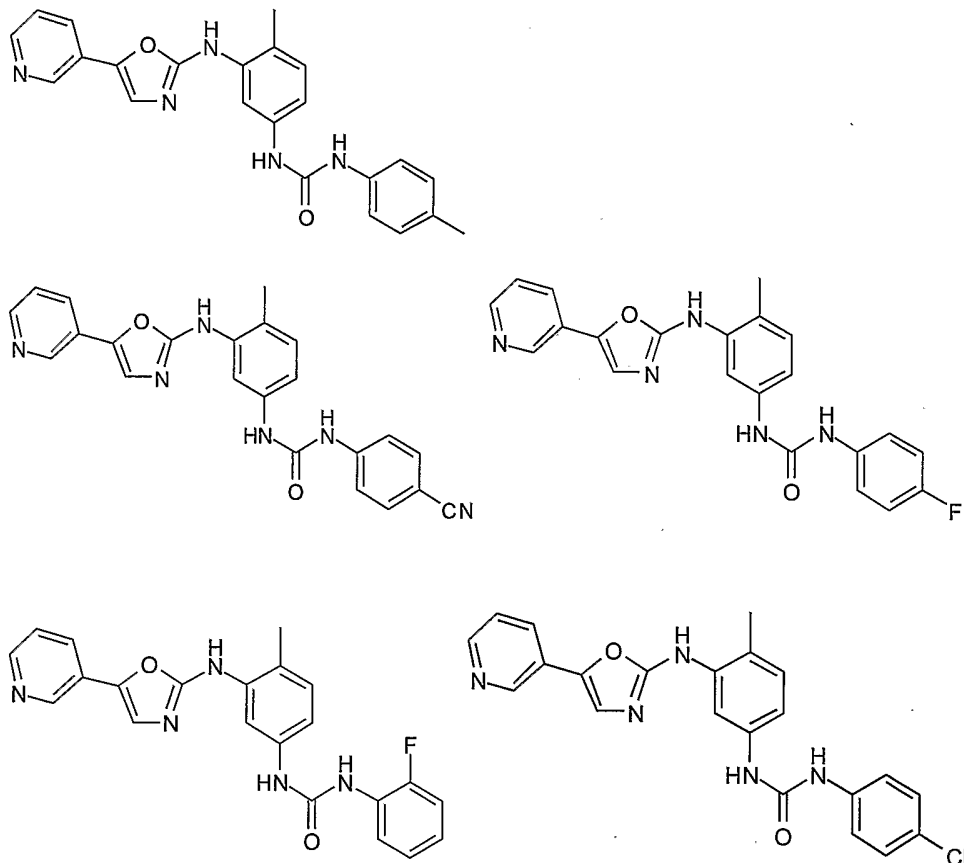
or a compound of formula XI-1:

10

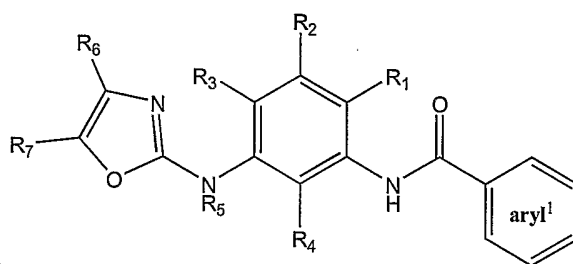


FORMULA XI-1

- wherein Ra, Rb are independently chosen from H or alkyl¹ or aryl¹ or heteroaryl¹,
 15 optionally substituted by a pendant basic nitrogen functionality, for example :



5 or a compound of formula XI-2:



FORMULA XI-2

wherein R₅ = H, Z is an aryl¹ group, aryl¹ being selected from :

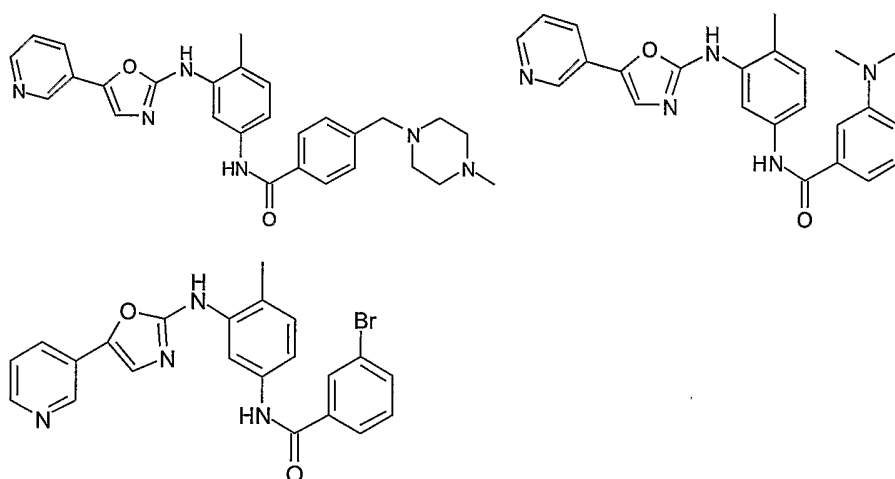
- a phenyl or a substituted variant thereof bearing any combination, at any one ring
- 10 position, of one or more substituents such as
- halogen(selected from I, F, Cl or Br);
 - an alkyl¹ group;

- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the

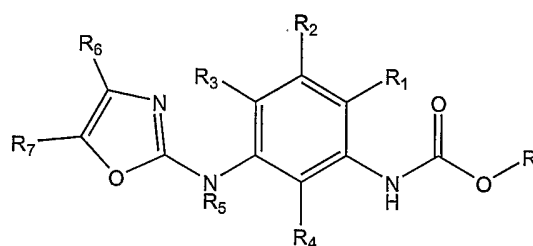
5

form of a basic nitrogen functionality;
 NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or
 COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹,
 aryl or heteroaryl, for example

10



or a compound of formula XI-3:



FORMULA XI-3

15 wherein R₅ = H and R is independently alkyl¹, aryl¹ or heteroaryl¹ as defined above.

Examples of compounds of Formula X :

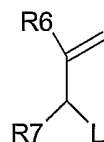
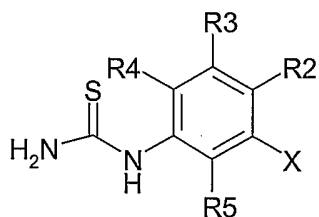
- 4- {[4-Methyl-3-(4-pyridin-3-yl-oxazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester
- 4-Methyl-N1-(5-pyridin-3-yl-oxazol-2-yl)-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine m.p.
- 5 4-Methyl-N1-(5-phenyl-oxazol-2-yl)-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- 4-Methyl-N1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- N1-Benzooxazol-2-yl-4-methyl-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- N-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-C-phenyl-methanesulfon -amide
- 10 N-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-acetamide
- 2-Cyano-N-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide
- 2-Ethoxy-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-acetamide
- 3-Methoxy-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-propionamide
- 1-(4-Cyano-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
- 15 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
- 1-(2-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
- 1-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea
- 1-(4-Chloro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
- 1-[4-Methyl-3-(5-phenyl-oxazol-2-ylamino)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea
- 20 1-(4-Cyano-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-thiourea
- 1-(4-Cyano-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-thiourea
- (2-{2-Methyl-5-[3-(4-trifluoromethyl-phenyl)-ureido]-phenylamino}-oxazol-5-yl)-acetic acid ethyl ester
- 1-Benzyl-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-thiourea
- 25 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-benzamide
- 3-Dimethylamino-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-benzamide
- 3-Bromo-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-benzamide
- N-[4-Methoxy-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

- 4-(3-Dimethylamino-propylamino)-*N*-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
N-[4-Fluoro-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
1*H*-Indole-6-carboxylic acid [4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amide
5 3-Isopropoxy-*N*-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-benzamide
N-[4-Methyl-3-(5-pyridin-2-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
3,5-Dimethoxy-*N*-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-benzamide
N-[3-(5-Pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
N-[4-Methyl-3-(5-phenyl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
10 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-*N*-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-benzamide
N-[4-Chloro-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
N-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-terephthalamide
5-Methyl-isoxazole-4-carboxylic acid [4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-
15 amide
4-Cyano-*N*-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-benzamide
N-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-isonicotinamide
N-[4-Methyl-3-(4-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester
20 (5-Isobutoxycarbonylamino-2-methyl-phenyl)-(5-pyridin-3-yl-oxazol-2-yl)-carbamic acid
isobutyl ester
[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester
N-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-2-*m*-tolyl-acetamide
2-(4-Fluoro-phenyl)-*N*-[4-methoxy-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide
25 2-(2,4-Difluoro-phenyl)-*N*-[4-methyl-3-(5-phenyl-oxazol-2-ylamino)-phenyl]-acetamide
2-(3-Bromo-phenyl)-*N*-[4-methyl-3-(5-pyridin-2-yl-oxazol-2-ylamino)-phenyl]-acetamide
3-(4-Fluoro-phenyl)-*N*-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-propionamide
N-{3-[5-(4-Cyano-phenyl)-oxazol-2-ylamino]-4-methyl-phenyl}-2-(2,4-difluoro-phenyl)-
acetamide
30 4-Methyl-pentanoic acid [4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-amide

- N*-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-2-piperazin-1-yl-acetamide
N-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-piperazin-1-yl-propionamide
 2-(2,6-Dichloro-phenyl)-*N*-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide
N-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-pyrrolidin-1-yl-propionamide
 5 *N*-[4-Methoxy-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-2-(4-trifluoromethyl-phenyl)-acetamide
 2-(4-Methoxy-phenyl)-*N*-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide
N-(4-Cyano-phenyl)-4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-benzamide
N-(3-Dimethylamino-phenyl)-4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-benzamide
 10 *N*-(2-Dimethylamino-ethyl)-4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-benzamide
N-(3-Fluoro-4-methyl-phenyl)-4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-benzamide
N-(3-Chloro-phenyl)-4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-benzamide
N-Benzyl-4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-benzamide
N-(4-Methoxy-benzyl)-4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-benzamide
 15 [4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-morpholin-4-yl-methanone
 [4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-piperazin-1-yl-methanone
N-(4-Fluoro-phenyl)-2-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide

Process for manufacturing a compound of formula III depicted above.

- 20 This entails the condensation of a substrate of general formula 10 with a thiourea of the type 11.



11 a: X = NH-R1

10

25

11 b: X = NH2

11 c: X = NH-PG

11 d: X = NO₂

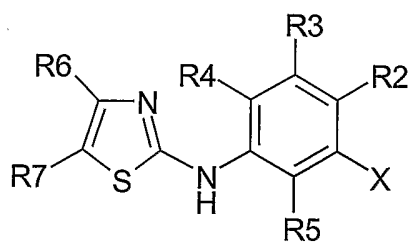
Substituent "L" in formula 10 is a nucleofugal leaving group in nucleophilic substitution reactions (for example, L can be selected from chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group).

Group R₁ in formula 11a corresponds to group R₁ as described in formula III.

Group "PG" in formula 11c is a suitable protecting group of a type commonly utilized by the person skilled in the art.

10

The reaction of 10 with 1 a-d leads to a thiazole-type product of formula **12a-d**.



12 a: X = NH-R₁

12 b: X = NH₂

12 c: X = NH-PG

12 d: X = NO₂

15

Formula 12a is the same as formula I. Therefore, R₁ in 12a corresponds to R₁ in formula III.

Formula 12b describes a precursor to compounds of formula III which lack substituent R₁. Therefore, in a second phase of the synthesis, substituent R₁ is connected to the free amine group in 12b, leading to the complete structure embodied by formula III:



The introduction of R₁, the nature of which is as described on page 3 for the general formula III, is achieved by the use of standard reactions that are well known to the

20

person skilled in the art, such as alkylation, acylation, sulfonylation, formation of ureas, etc.

5 Formula 12c describes an N-protected variant of compound 12b. Group "PG" in formula 12c represents a protecting group of the type commonly utilized by the person skilled in the art. Therefore, in a second phase of the synthesis, group PG is cleaved to transform compound 12c into compound 12b. Compound 12b is subsequently advanced to structures of formula I as detailed above.

10 Formula 12d describes a nitro analogue of compound 12b. In a second phase of the synthesis, the nitro group of compound 12d is reduced by any of the several methods utilized by the person skilled in the art to produce the corresponding amino group, namely compound 12b. Compound 12b thus obtained is subsequently advanced to structures of formula III as detailed above.

15

Examples of compound synthesis is found in our previous applications WO 2004/014903 and US 60/513,214, incorporated herein by reference.

20 The expression HIV related diseases as referred herein includes the following therapeutic applications: all forms of human immunodeficiency virus type 1, type 2, acquired immunodeficiency syndrome, AIDS-related non-Hodgkin's lymphomas including aggressive monoclonal B-cell Burkitt's lymphomas, large cell lymphomas, immunoblastic lymphomas and Kaposi's sarcoma, neurological disorders such as dementia, opportunistic infections such as candida, oral hairy leukoplakia, herpes zoster
25 (shingles), bacillary angiomatosis and tuberculosis, bone disorders such as osteoporosis and osteopenia, progressive cytopenias (anemia, thrombocytopenia, leukopenia).

In a further embodiment, c-kit inhibitors as mentioned above are inhibitors of wild type or mutant activated c-kit. In this regard, the invention contemplates a method for treating HIV infection and related diseases as defined above comprising administering to a human in need of such treatment a compound that is a selective, potent and non toxic inhibitor of c-kit obtainable by a screening method which comprises :

- a) bringing into contact (i) activated c-kit and (ii) at least one compound to be tested; under conditions allowing the components (i) and (ii) to form a complex,
- b) selecting compounds that inhibit activated c-kit,
- c) testing and selecting a subset of compounds identified in step b), which are unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

This screening method can further comprise the step consisting of testing and selecting a subset of compounds identified in step b) that are inhibitors of mutant activated c-kit (for example in the transphosphorylase domain), which are also capable of inhibiting SCF-activated c-kit wild. Alternatively, in step a) activated c-kit is SCF-activated c-kit wild.

A best mode for practicing this method consists of testing putative inhibitors at a concentration above 10 μ M in step a). In step c), IL-3 is preferably present in the culture media of IL-3 dependent cells at a concentration comprised between 0.5 and 10 ng/ml, preferably between 1 to 5 ng/ml. These screening may be performed following our previous application WO 03/003006, which is incorporated herein by reference.

Therefore, the invention embraces the use of the compounds defined above to manufacture a medicament for treating of all forms of human immunodeficiency virus type 1, type 2, treating or delaying the onset of acquired immunodeficiency syndrome, including AIDS-related non-Hodgkin's lymphomas including aggressive monoclonal B-cell Burkitt's lymphomas, large cell lymphomas, immunoblastic lymphomas and Kaposi's sarcoma, neurological disorders such as dementia, opportunistic infections such

as candida, oral hairy leukoplakia, herpes zoster (shingles), bacillary angiomatosis and tuberculosis, bone disorders such as osteoporosis and osteopenia, progressive cytopenias (anemia, thrombocytopenia, leukopenia).

- 5 The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, sublingual, or rectal means.
- 10 In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack
- 15 Publishing Co., Easton, Pa.).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated

20 as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

More particularly, the invention relates to a pharmaceutical composition intended for oral administration.

25

Pharmaceutical compositions suitable for use in the invention include compositions wherein compounds for depleting mast cells, such as c-kit inhibitors, or compounds

inhibiting mast cells degranulation are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50. Pharmaceutical compositions which exhibit large therapeutic indices are preferred.

Example 1 : AB compounds of formula III, IV, V and X are selective and potent c-Kit and mast cell inhibitors.

The specific compounds as listed above are non limitative illustrative examples of AB compounds. They display IC50 below 5 μ M, 1 μ M or even 0.1 μ M on different forms of c-KIT (Figure 1). Also, these AB compounds are selective for c-KIT versus other tyrosine kinases (Table 1).

Table 1 : Inhibition of various protein tyrosine kinases by the AB compound *in vitro*

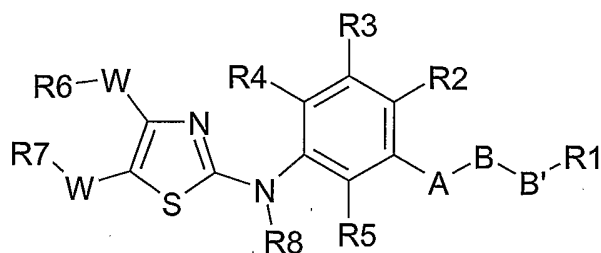
Enzyme / Cell line	IC50 [μ M]
In vitro enzymatic assay on purified kinases	
c-Kit	0.01
PDGF-beta	0.49
ABL1	5.7
VEGFR1	IC50 > 100
EGFR	IC50 > 100
FGFR1	IC50 > 100
FLT3	IC50 > 100
JAK2	IC50 > 100
AKT1	57
PKC-alpha	100
SRC	IC50 > 100
IGF1R	IC50 > 100
PIM1	19

In addition, the AB compounds potently and dose-dependently inhibited the growth of the mast cells (MC) when they were cultured in the presence of SCF (with an IC₅₀ of <0.1 μ M). Again these in vitro data confirmed the potent and selective inhibitory activity
5 of c-Kit tyrosine kinase activity as well as the ability of the AB compound to inhibit almost completely the survival of MC population at concentration lower than 0.1 μ M. AB compounds have also been shown to deplete mast cells in vivo. The AB compound has successfully completed preclinical development in September 2003. Safety pharmacology studies revealed no significant effects of the AB compound on the central
10 nervous, cardiovascular and respiratory systems.

CLAIMS

- 5 1. A method for treating HIV infection and related diseases, including human immunodeficiency virus type 1 and 2, or delaying the onset of acquired immunodeficiency syndrome (AIDS), comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cells degranulation in a human in need of such treatment.
- 10 2. The method according to claim 1 for treating patients suffering from HIV infection and related diseases comprising administering a c-kit inhibitor to a human in need of such treatment.
- 15 3. The method according to claim 2, wherein said c-kit inhibitor is a non-toxic, selective and potent c-kit inhibitor wherein it is unable to promote death of IL-3 dependent cells cultured in presence of IL-3.
- 20 4. The method according to claim 1 or 3 wherein said inhibitor is selected from the group consisting of :
- 2-(3-Substitutedaryl)amino-4-aryl-thiazoles such as 2-(3-amino)arylamino-4-aryl-thiazoles,
 - 2-aminoaryloxazoles,
 - pyrimidine derivatives, more particularly N-phenyl-2-pyrimidine-amine derivatives,
 - 25 - indolinone derivatives, more particularly pyrrol-substituted indolinones,
 - monocyclic, bicyclic aryl and heteroaryl compounds,
 - and quinazoline derivatives.

5. The method according to claim 4, wherein said c-kit inhibitor is selected from compounds belonging to the 2-(3-Substitutedaryl)amino-4-aryl-thiazoles of **formula III**:



FORMULA III

5

wherein

R⁶ and **R⁷** are independently from each other chosen from one of the following:

i) hydrogen, a halogen (selected from F, Cl, Br or I),

ii) an **alkyl¹** group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms, or from 2 or 3 to 10 carbon atoms, (for example methyl, ethyl, propyl, butyl, pentyl, hexyl...) and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl, cyano, nitro, formyl;

15 (iii) an **aryl¹** group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as

- halogen(selected from I, F, Cl or Br);
- an **alkyl¹** group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-**alkyl¹**, carboxyl, cyano, nitro, formyl, hydroxy, NH-**alkyl¹**, N(**alkyl¹**)(**alkyl¹**), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;

20

(iv) a **heteroaryl**¹ group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as

- 5 - halogen (selected from F, Cl, Br or I);
- an alkyl¹ group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹,
- 10 N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;

(v) trifluoromethyl, carboxyl, cyano, nitro, formyl, hydroxy, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality.

15

R⁸ is one of the following:

- (i) hydrogen, or
- (ii) a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I),
- 20 oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
- (iii) CO-R₈ or COOR₈ or CONHR₈ or SO₂R₈ wherein R₈ may be
 - a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F,
 - 25 Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
 - an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen

(selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a pendant basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or

- a heteroaryl group such as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinoliny group, which may additionally bear any combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

25

R2, R3, R4 and R5 each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen

(selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group
 5 containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

A is : CH₂, O, S, SO₂, CO, or COO,

10 B is a bond or NH, NCH₃, NR*, (CH₂)_n (n is 0, 1 or 2), O, S, SO₂, CO, or COO,

B' is a bond or NH, NCH₃, NR*, (CH₂)_n (n is 0, 1 or 2), O, S, SO₂, CO or COO;

R* being an alkyl¹, aryl¹ or heteroaryl¹

W is a bond or a linker selected from NH, NHCO, NHCOO, NHCONH, NHSO₂, NHSO₂NH, CO, CONH, COO, COCH₂, (CH₂)_n (n is 0, 1 or 2), CH₂-CO, CH₂COO,

15 CH₂-NH, O, OCH₂, S, SO₂, and SO₂NH

R¹ is :

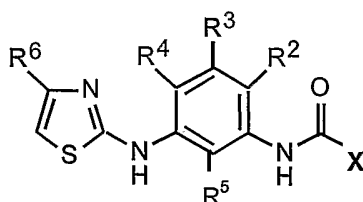
a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F,
 20 and / or bearing a pendant basic nitrogen functionality;

b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality

c) an alkyl¹, aryl¹ or heteroaryl¹.

25

6. A method according to claim 5, wherein said c-kit inhibitor is selected from compounds of formula V :



FORMULA V

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, a heteroaryl, an alkyl, or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, a heteroaryl, an alkyl or a cycloalkyl group substituted with an aryl, a heteroaryl, an alkyl or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,

R² is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R³ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁴ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

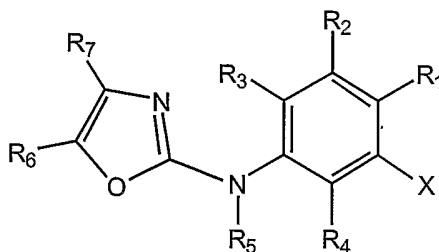
R⁵ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R⁶ is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH₂, NO₂ or SO₂-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

7. The method according to claim 4, wherein said c-kit inhibitor is selected from 2-aminoaryloxazoles of formula X :



FORMULA X

wherein substituents R₁ - R₇ and X are defined as follows:

R₁, R₂, R₃ and R₄ each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a

pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one
5 heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

R5 is one of the following:

- (i) hydrogen, or
- 10 (ii) a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
- (iii) CO-R8 or COOR8 or CONHR8 or SO₂R8 wherein R8 may be
 - 15 - a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
 - an aryl group such as phenyl or a substituted variant thereof bearing any
20 combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro,
25 formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a pendant basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at

least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or

- a heteroaryl group such as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as halogen (selected from F, Cl, Br or I), alkyl groups containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

R₆ and R₇ each independently are selected from:

- i) hydrogen, a halogen (selected from F, Cl, Br or I), or
- ii) an **alkyl**¹ group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl, cyano, nitro, formyl; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic

nitrogen functionality ; as well as a cycloalkyl or aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality, or

(iii) an **aryl**¹ group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as

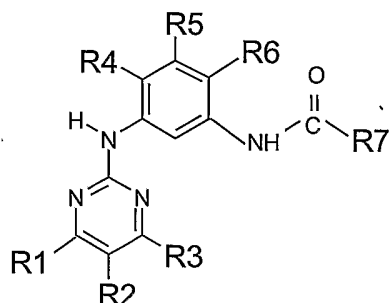
- 5 - halogen(selected from I, F, Cl or Br);
- an alkyl¹ group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹,
10 N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl, or
- 15 (iv) a **heteroaryl**¹ group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, indolyl, benzimidazole, quinoliny group, which may additionally bear any combination, at any one ring position, of one or more substituents such as
 - halogen (selected from F, Cl, Br or I);
 - 20 - an alkyl¹ group;
 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
 - trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the
25 form of a basic nitrogen functionality;
 - NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, or

- (v) an O-aryl¹, or NH-aryl¹, or O-heteroaryl¹ or NH-heteroaryl¹ group
(vi) trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality, or
- 5 (vi) NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl.

X is:

- 10 -NR₉R₁₀, wherein R₉ and / or R₁₀ are hydrogen or:
- i) an alkyl¹ group, CF₃ or
 - ii) an aryl¹, heteroaryl¹ or cycloalkyl group optionally substituted by a a pendant basic nitrogen functionality, or
 - iii) a CO-R, COO-R, CON-RR' or SO₂-R, where R and R' are a hydrogen, alkyl¹, aryl¹
- 15 or heteroaryl¹, optionally substituted by a a pendant basic nitrogen functionality;
- or:
- CO-NR₉R₁₀, wherein R₉ and / or R₁₀ are hydrogen or:
- i) an alkyl¹ group, CF₃ or
 - ii) an aryl¹, heteroaryl¹ or cycloalkyl group optionally substituted by a a pendant basic
- 20 nitrogen functionality.

8. The method according to claim 4, wherein said inhibitor is selected from the group consisting of N-phenyl-2-pyrimidine-amine derivatives having the formula II :



wherein R1, R2 and R3 are independently chosen from H, F, Cl, Br, I, a C1-C5 alkyl or a cyclic or heterocyclic group, especially a pyridyl group;

R4, R5 and R6 are independently chosen from H, F, Cl, Br, I, a C1-C5 alkyl, especially a methyl group;

and R7 is a phenyl group bearing at least one substituent, which in turn possesses at least one basic site, such as an amino function.

9. The method according to claim 8, wherein said inhibitor is the 4-(4-méthylpipérazine-1-ylméthyl)-N-[4-méthyl-3-(4-pyridine-3-yl)pyrimidine-2 ylamine]phényl]-benzamide.

10. A method for treating HIV infection or delaying the onset of AIDS comprising administering to a human in need of such treatment a compound that is a selective, potent and non toxic inhibitor of activated c-kit obtainable by a screening method which comprises :

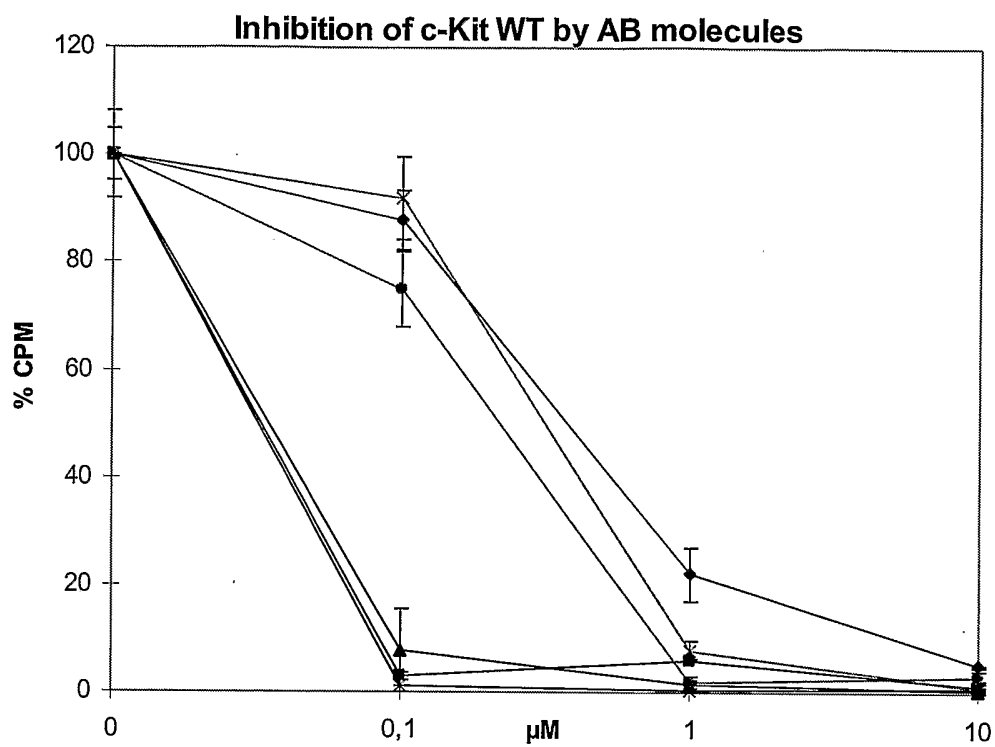
- a) bringing into contact (i) activated c-kit and (ii) at least one compound to be tested; under conditions allowing the components (i) and (ii) to form a complex,
- b) selecting compounds that inhibit activated c-kit,
- c) testing and selecting a subset of compounds identified in step b), which are unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

11. The method according to one of claims 1 to 10 for treating of all forms of human immunodeficiency virus type 1, type 2, for treating or delaying the onset of acquired

immunodeficiency syndrome, including AIDS-related non-Hodgkin's lymphomas including aggressive monoclonal B-cell Burkitt's lymphomas, large cell lymphomas, immunoblastic lymphomas and Kaposi's sarcoma, neurological disorders such as dementia, opportunistic infections such as candida, oral hairy leukoplakia, herpes zoster
5 (shingles), bacillary angiomatosis and tuberculosis, bone disorders such as osteoporosis and osteopenia, progressive cytopenias (anemia, thrombocytopenia, leukopenia).

12. The use of a compound as defined in one of claims 1 to 9 or obtainable by the method of claim 10 to manufacture a medicament for treating of all forms of human
10 immunodeficiency virus type 1, type 2, treating or delaying the onset of acquired immunodeficiency syndrome, including AIDS-related non-Hodgkin's lymphomas including aggressive monoclonal B-cell Burkitt's lymphomas, large cell lymphomas, immunoblastic lymphomas and Kaposi's sarcoma, neurological disorders such as dementia, opportunistic infections such as candida, oral hairy leukoplakia, herpes zoster
15 (shingles), bacillary angiomatosis and tuberculosis, bone disorders such as osteoporosis and osteopenia, progressive cytopenias (anemia, thrombocytopenia, leukopenia).

1 / 1

**FIGURE 1**

INTERNATIONAL SEARCH REPORT

Interr al Application No
PC1/182005/001433

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/404 A61K31/421 A61K31/425 A61K31/506 A61K31/517
A61P31/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOON H B ET AL: "Imatinab mesylate in AIDS-related Kaposi's sarcoma" PROC AM SOC CLIN ONCOL, 'Online! vol. 22, 2003, pages 195-195, XP002338472 Retrieved from the Internet: URL: http://www.asco.org/ac/1,1003,_12-002636-00_18-0023-00_19-00103219,00.asp 'retrieved on 2005-07-28! abstract 782	1-4,8-12
X	WO 03/072090 A (AB SCIENCE; MOUSSY, ALAIN; KINET, JEAN-PIERRE) 4 September 2003 (2003-09-04)	1-4,8-12
Y	page 5, line 22 - page 7, line 19; page 8, line 4-15	1-4,8-12
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☒ 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

3 August 2005

Date of mailing of the international search report

22/08/2005

Name and mailing address of the ISA

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Borst, M

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/IB2005/001433

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/002105 A (AB SCIENCE; MOUSSY, ALAIN; KINET, JEAN-PIERRE) 9 January 2003 (2003-01-09) page 4, line 10 - page 5, line 5; page 6, line 11-21	1-4,8-12
Y	----- HE JIANGLIN ET AL: "Astrocyte apoptosis induced by HIV-1 transactivation of the c-kit protooncogene" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 94, no. 8, 1997, pages 3954-3959, XP002338622 ISSN: 0027-8424 page 3957-3959, paragraph entitled "Discussion"	1-12
Y	----- LONGLEY B J ET AL: "NEW APPROACHES TO THERAPY FOR MASTOCYTOSIS A CASE FOR TREATMENT WITH KIT KINASE INHIBITORS" HEMATOLOGY - ONCOLOGY CLINICS OF NORTH AMERICA, W.B. SAUNDERS, US, vol. 14, no. 3, June 2000 (2000-06), pages 689-695, XP008010967 ISSN: 0889-8588 page 694, paragraph entitled "Summary"	1-4,8-12
Y	----- WO 2004/014903 A (AB SCIENCE; CIUFOLINI, MARCO; WERMUTH, CAMILLE; GIELTHEN, BRUNO; MOUSS) 19 February 2004 (2004-02-19) claim 1-18	5,6
Y	----- WO 03/003006 A (AB SCIENCE; INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE) 9 January 2003 (2003-01-09) cited in the application page 5, line 10-17	10
P,Y	----- WO 2004/032882 A (SMITHKLINE BEECHAM CORPORATION; BROWN, MATTHEW, LEE; CHEUNG, MUI; DICK) 22 April 2004 (2004-04-22) examples on pages 69-187	7
E	----- WO 2005/040139 A (AB SCIENCE; CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE ; INSTITUT CU) 6 May 2005 (2005-05-06) cited in the application page 49, line 16, 18; claim 1-12	1-4,7-12

INTERNATIONAL SEARCH REPORT

I - ational application No.
- PCT/IB2005/001433

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy: Although claims 1-11 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 compound/composition.
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

Information on patent family members

International Application No

PCT/IB2005/001433

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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