Title: USE OF C-KIT INHIBITORS FOR TREATING FIBROSIS

Abstract: The present invention relates to a method for treating fibrosis and related disorders comprising administering a compound capable of depleting mast cell or a compound inhibiting mast cells 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 II.3 dependent cells cultured in presence of II.3.
Use of c-kit inhibitors for treating Fibrosis

The present invention relates to a method for treating fibrosis and related disorders comprising administering a compound capable of depleting mast cell or a compound inhibiting mast cells 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 cultured in presence of IL-3.

Cystic fibrosis (CF) is a lung, digestive, and reproductive systems genetic disease affecting 0.4% of the population. Glands produce abnormally thick mucus, saliva, and intestinal fluids which are responsible for breathing problems, infections, and lung damage. Thick secretions also may clog the pancreatic duct and block transfer of enzymes from the pancreas to the intestine. These enzymes help break down food so the body has proper growth and weight gain. This disorder also alters fertility in male and female. The mechanism of action for airway inflammation in cystic fibrosis remains poorly understood and there is no cure as of today. Palliative treatments include drugs to restore salt and water balance, antibiotics for lung infection, inhaled beta-adrenergic agonists and enzymes. Patients show progressive respiratory failure due to impaired mucus clearance and bacteria infection in the airways. They have an average life expectancy of about 30 years.

Thus, there is an urgent need for a treatment for cystic fibrosis.

Inflammatory cells have been associated with fibrotic disorders. For example, pulmonary fibrosis is thought to be due to the destructive effects of leukocytes (Marshall et al., Int. J
Biochem. Cell Bio., 1997, 29:107-120 as well as the recruitment and activation of lymphocytes (Schrier, D. J. et al., Am. J. Pathol, 1984, 116:270-278). Pulmonary fibrosis and atherosclerosis have many similarities at the histopathologic level. Moreover, fibrotic lung diseases exhibit systemic effects and have the potential to affect the vasculature beyond the lung. Consequently, a treatment for cystic fibrosis could also be indicated for coronary artery disease, and atherosclerosis, more generally to all vascular fibrosis disorders.

Anticytokine therapeutic approaches have been more recently suggested for treating fibrosis. But, instead of focusing on particular detrimental cytokines, which specific role remains to be elucidated, we propose here to deplete or inactivate mast cells that are from our experience the key of the inflammatory immune system.

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 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 non hematopoietic cells.

“Normal” MC activation is followed by the controlled release a variety of mediators that are essential for the organism. By contrast, in case of hyperactivation of MCs, uncontrolled hypersecretion of these mediators is deleterious for the body. Mast cells produce a large variety of mediators categorized into three groups: preformed granule-associated mediators (histamine, proteoglycans, and neutral proteases), lipid-derived
mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, GM-CSF, MIP-1α, MIP-1β and IFN-γ), most of them having strong pro-inflammatory activities. For instance, a massive release of MCs mediators is responsible for anaphylactic reactions that could be sometimes fatal to the patients and are always responsible for a significant morbidity. Since MCs are distributed in almost all the body sites, hypersecretion of mediators by activated elements can lead to multiple organ failures.

More specifically, there are several are fibrogenic cytokines, including platelet-derived growth factor, transforming growth factor-beta (TGF beta) and basic fibroblast growth factor (bFGF) but also protease including chymase and tryptase that we suspect as being directly involved in fibrotic processes.

Furthermore, histamine and tryptase were found to participate in the increase in fibroblast proliferation and collagen production. Basic fibroblast growth factor (bFGF) is a potent mitogenic factor for smooth muscle cells, myofibroblasts, and fibroblasts, proliferation of which is a hallmark of idiopathic pulmonary fibrosis (IPF) and lymphangioleiomyomatosis (LAM). Chymase secreted by mast cells found in fibroblast-containing interstitial connective tissue has been implicated in collagen fiber formation and extracellular matrix production and has been shown to promote myocardial and renal interstitial fibrosis by converting angiotensin I to II. At last, we observe an increase in mast cell count in fibrotic patients.

Then, liberation by activated mast cells of the above fibrogenic mediators, which acts in consort, contributes to the proliferation of fibroblasts and other cells, ultimately promoting collagen synthesis and extracellular matrix production leading to tissue remodelling and fibrosis in different tissues.
Besides, in connection with the present invention, we have unexpectedly discovered that c-kit inhibitors could be a new route for treating fibrosis since our inhibitors allow to destroy mast cells and thus impede the release of cytokines and growth factors cocktail inducing fibroblasts, vascular smooth muscle cells and endothelial cells proliferation.

Description

The present invention relates to a method for treating fibrosis and related disorders comprising administering a compound capable of depleting mast cells or blocking mast cells degranulation to a human in need of such treatment.

Said method for treating fibrosis and related diseases 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, selenoindoles, selenides, tricyclic polyhydroxylic compounds and benzylphosphonic acid compounds.

Among preferred compounds, it is of interest to focus on pyrimidine derivatives such as 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

So, preferably, the invention relates to a method for treating fibrosis 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:

![Chemical Structure](image)

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:
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.

Preferably, R7 is the following group:

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,

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 fibrosis and related disorders comprising the administration of an effective amount of the compound known in the art as CGP57148B:

\[
4-(4\text{-methylpiperazine-1-ylmethyl})-N-[4\text{-methyl-3-(4-pyridine-3-yl)pyrimidin-2-ylamino}ph\text{eny}l]-benzamide
\]

The preparation of this compound is described in example 21 of EP 564 409 and the \( \beta \)-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 \( 2-(3\text{-Substitutedaryl})amino-4\text{-aryltiazoles} \) such as those for which the applicant filed PCT/IB2005/000401, incorporated herein by reference, especially compounds of \textbf{formula III}:

\[
\text{FORMULA III}
\]

wherein

\( R^6 \) and \( R^7 \) are independently from each other chosen from one of the following:
i) hydrogen, a halogen (selected from F, Cl, Br or I),

ii) an alkyl\(^1\) 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;

(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;
- trifluoromethyl, O-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;

(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

- halogen (selected from F, Cl, Br or I);
- an alkyl\(^1\) group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
(v) trifluoromethyl, carboxyl, cyano, nitro, formyl, hydroxy, N(alkyl)\(^1\)(alkyl)\(^1\), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality.

R\(^8\) 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-R\(^8\) or COOR\(^8\) or CONHR\(^8\) or SO2R\(^8\) wherein R\(^8\) 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, C\(_1\)-alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C\(_1\)-alkylamino, di(C\(_1\)-alkyl)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 heteroeatoms 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 heteroeatoms 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
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:
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) an alkyl1, aryl1 or heteroaryl1.

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.

For example, a subset of compounds may correspond to

![Chemical structure](image)

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

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

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 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.
- 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.
- 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.

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:

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\[
\begin{array}{c}
\text{R}^6 \quad \text{R}^7 \quad \text{N} \quad \text{S} \\
\text{R}^4 \quad \text{R}^3 \quad \text{R}^2 \\
\text{N} \quad \text{R}^1
\end{array}
\]
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**FORMULA IV**

5 and wherein \( R^1 \) 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;

\( R^2 \) 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;

\( R^4 \) 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 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;
(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;
and R' 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.

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.

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 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 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;
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 and / 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, 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:

![Chemical Structure](image)

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 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 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 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 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 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 NHCOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms 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 NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms 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 NHCONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms 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 a heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an \( \text{OSO}_2R \), where \( R \) is a linear or branched alkyl group containing from 1 to 10 carbon atoms 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 a heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an \( \text{NRaOSO}_2\text{Rb} \), where \( \text{Ra} \) and \( \text{Rb} \) are a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; \( \text{Ra} \) 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 a heteroatom, notably a halogen selected from I, Cl, Br and F, and / or 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;

\( R^3 \) 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 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;

(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; 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, Br and F, and / or bearing a pendant basic nitrogen functionality;

and $R^7$ 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, 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.

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 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,

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.

In another alternative, substituent R6, 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 independently 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 R⁵ is a 3-pyridyl group.
2- A compound of formula V as depicted above, wherein X is group d and R^4 is a methyl group.

3- A compound of formula III or IV as depicted above, wherein R^1 is group d and R^2 and/or R^3 and/or R^5 is H.

4- A compound of formula III or IV as depicted above, wherein R^6 is a 3-pyridyl group and R^4 is a methyl group.

5- A compound of formula III or IV as depicted above, wherein R^2 and/or R^3 and/or R^5 is H and R^4 is a methyl group.

6- A compound of formula III or IV as depicted above wherein R^2 and/or R^3 and/or R^5 is H, R^4 is a methyl group and R^6 is a 3-pyridyl group.

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

![Chemical Structure](image)

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; or a 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
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.

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 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;

(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.

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.

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
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
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-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
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-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
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
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

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:

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;
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 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;

(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.

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
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3-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
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-Dirfluoromethoxy-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
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
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
4-(3-[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
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
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
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

20 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

25 3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide
34

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
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
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
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 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

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

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

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

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

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
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
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
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 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](image)

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 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.

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:

![Chemical Structure](image)

**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, C1₄alkyloxy, amino, C₄ alkylamino, di(C1₄alkyl)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, C₁₋₄alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₄alkylamino, di(C₁₋₄alkyl)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, thiienyl, 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, C₁₋₄alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₄alkylamino, di(C₁₋₄alkyl)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 alkyl¹ 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 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-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), 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, alkyl\(^1\), aryl or heteroaryl, or

(iv) a **heteroaryl**\(^1\) group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thieryl, 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);
- an alkyl\(^1\) group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
- trifluoromethyl, O-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), 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, alkyl\(^1\), or

(v) an O-aryl\(^1\), or NH-aryl\(^1\), or O-heteroaryl\(^1\) or NH-heteroaryl\(^1\) group

(vi) trifluoromethyl, O-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality, or

(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, alkyl\(^1\), 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 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 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
nitrogen functionality.

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

![Chemical Structure](image)

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:

![Chemical Structure](image)

**FORMULA XI**

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 alkyl or aryl or heteroaryl, optionally substituted by a pendant basic nitrogen functionality, for example:

![Chemical Structure](image)

or a compound of formula XI-1:

![Chemical Structure](image)

**FORMULA XI-1**

wherein Ra, Rb are independently chosen from H or alkyl or aryl or heteroaryl, optionally substituted by a pendant basic nitrogen functionality, for example:
or a compound of formula XI-2:

FORMULA XI-2

wherein R5 = H, Z is an aryl\(^1\) group, aryl\(^1\) being selected from:
a 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;
- trifluoromethyl, O-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), 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, alkyl\(^1\), aryl or heteroaryl, for example

![Chemical structures](image)

or a compound of formula XI-3:

**FORMULA XI-3**

15 wherein R5 = H and R is independently alkyl\(^1\), aryl\(^1\) or heteroaryl\(^1\) 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  
4-Methyl-N1-(5-phenyl-oxazol-2-yl)-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine  
N1-Benzooxazol-2-y1-4-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-methanesulfonamide  
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  
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  
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  
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
1H-Indole-6-carboxylic acid [4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amide
3-Isopropanoyl-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
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]-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
(5-Isobutoxy carbonylamino)-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]-2-4-tolyl-acetamide
2-(4-Fluoro-phenyl)-N-[4-methoxy-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide
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
4-Methyl-pentanoic acid [4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-amide
\textbf{Process for manufacturing a compound of formula III depicted above.}

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

\begin{align*}
11\ a: & \quad X = \text{NH-R1} \\
11\ b: & \quad X = \text{NH}_2 \\
11\ c: & \quad X = \text{NH-PG}
\end{align*}
11 d: \( X = \text{NO}_2 \)

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.

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

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:

\[ 12b + \text{“R1”} \rightarrow \text{III} \]

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

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.

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.

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

The expression fibrosis as referred herein includes the following potential therapeutic applications: all forms of AA and AL renal amyloidosis, idiopathic pulmonary fibrosis, drug induced pulmonary fibrosis, cystic fibrosis, peritoneal adhesion, pancreatic fibrosis, Uterine leiomyoma, renal interstitial fibrosis after allografted kidney transplantation, liver fibrosis, dermal fibrosis.

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 treating fibrosis and related disorders 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 µM 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 preventing and/or treating fibrosis including all forms of
AA and AL renal amyloidosis, idiopathic pulmonary fibrosis, drug induced pulmonary
fibrosis, cystic fibrosis, peritoneal adhesion, pancreatic fibrosis, Uterine leiomyoma,
renal interstitial fibrosis after allografted kidney transplantation, liver fibrosis, dermal
fibrosis, vascular fibrosis as well as coronary artery disease and atherosclerosis.

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.

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 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 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.

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 µM, 1 µM or even 0.1 µM 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

<table>
<thead>
<tr>
<th>Enzyme / Cell line</th>
<th>IC50 [µM]</th>
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<tbody>
<tr>
<td>In vitro enzymatic assay on purified kinases</td>
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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 µM). Again these in vitro data confirmed the potent and selective inhibitory activity 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 µM. 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 nervous, cardiovascular and respiratory systems.
CLAIMS

1. A method for treating fibrosis and related disorders, comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cells degranulation in a human in need of such treatment.

2. The method according to claim 1 for treating patients suffering from fibrosis comprising administering a c-kit inhibitor to a human in need of such treatment.

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.

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-aminoarylthiazoles,
   - pyrimidine derivatives, more particularly N-phenyl-2-pyrimidine-amine derivatives,
   - 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:

![Chemical structure formula III](attachment:formula.png)

FORMULA III

wherein

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

1. **hydrogen, a halogen (selected from F, Cl, Br or I),**
2. **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;**
3. **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;
(iv) a heteroaryl 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);
- an alkyl group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
- trifluoromethyl, O-alkyl, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl, N(alkyl)(alkyl), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
(v) trifluoromethyl, carboxyl, cyano, nitro, formyl, hydroxy, N(alkyl)(alkyl), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality.

R^8 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-R^8 or COOR^8 or CONHR^8 or SO2R^8 wherein R^8 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, C₁₋₅alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₅alkylamino, di(C₁₋₅alkyl)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, C₁₋₅alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₅alkylamino, di(C₁₋₅alkyl)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, C\textsubscript{1-6}alkyloxy, amino, C\textsubscript{1-6}alkylamino, di(C\textsubscript{1-6}alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, CONH-R, SO\textsubscript{2}-R, and SO\textsubscript{2}NH-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 : CH\textsubscript{2}, O, S, SO\textsubscript{2}, CO, or COO,

B is a bond or NH, NCH\textsubscript{3}, NR\textsuperscript{*}, (CH\textsubscript{2})\textit{n} \textit{n} is 0, 1 or 2), O, S, SO\textsubscript{2}, CO, or COO,

B' is a bond or NH, NCH\textsubscript{3}, NR\textsuperscript{*}, (CH\textsubscript{2})\textit{n} \textit{n} is 0, 1 or 2), O, S, SO\textsubscript{2}, CO, or COO;

R\textsuperscript{*} being an alkyl\textsuperscript{1}, aryl\textsuperscript{1} or heteroaryl\textsuperscript{1}

W is a bond or a linker selected from NH, NHCO, NHCOO, NHCONH, NHSO\textsubscript{2}, NHSO\textsubscript{2}OH, CO, CONH, COO, COCH\textsubscript{2}, (CH\textsubscript{2})\textit{n} \textit{n} is 0, 1 or 2), CH\textsubscript{2}-CO, CH\textsubscript{2}COO, CH\textsubscript{2}-NH, O, OCH\textsubscript{2}, S, SO\textsubscript{2}, and SO\textsubscript{2}NH

R\textsuperscript{1} 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) an alkyl\textsuperscript{1}, aryl\textsuperscript{1} or heteroaryl\textsuperscript{1}.

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:

```
\begin{center}
\includegraphics[width=0.5\textwidth]{formula}
\end{center}
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**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, C₁₋₅alkyloxy, amino, C₁₋₅alkylamino, di(C₁₋₅alkyl)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 COO-R₈ or CONH-R₈ or SO₂-R₈ 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, C₁₋₅alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₋₅alkylamino, di(C₁₋₅alkyl)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, C_{1-6}alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)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 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** 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 group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl, N(alkyl)(alkyl), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHCO-R or NHC00-R or NHCONH-R or NHSO2-R or NHS02NH-R or CO-R or COO-R or CONH-R or SO2-R or SO2NH-R wherein R corresponds to hydrogen, alkyl, aryl or heteroaryl, or

(iv) a **heteroaryl** 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);
- an alkyl group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
- trifluoromethyl, O-alkyl, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl, N(alkyl)(alkyl), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHCO-R or NHC00-R or NHCONH-R or NHSO2-R or NHS02NH-R or CO-R or COO-R or CONH-R or SO2-R or SO2NH-R wherein R corresponds to hydrogen, alkyl, or
(v) an O-aryl\(^1\), or NH-aryl\(^1\), or O-heteroaryl\(^1\) or NH-heteroaryl\(^1\) group
(vi) trifluoromethyl, O-alkyl\(^1\), carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\(^1\), N(alkyl\(^1\))(alkyl\(^1\)), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality, or
(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, alky1\(^1\), aryl or heteroaryl.

X is:

- NR9R10, wherein R9 and / or R10 are hydrogen or:
  i) an alky1\(^1\) group, CF3 or
  ii) an aryl\(^1\), heteroaryl\(^1\) 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, alky1\(^1\), aryl\(^1\) or heteroaryl\(^1\), optionally substituted by a a pendant basic nitrogen functionality;

or:

- CO-NR9R10, wherein R9 and / or R10 are hydrogen or:
  i) an alky1\(^1\) group, CF3 or
  ii) an aryl\(^1\), heteroaryl\(^1\) or cycloalkyl group optionally substituted by a a pendant basic 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 ylamino]phényl]-benzamide.

10. A method for treating treating fibrosis and related disorders 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 for preventing and/or treating fibrosis including all forms of AA and AL renal amyloidosis, idiopathic
pulmonary fibrosis, drug induced pulmonary fibrosis, cystic fibrosis, peritoneal adhesion, pancreatic fibrosis, Uterine leiomyoma, renal interstitial fibrosis after allografted kidney transplantation, liver fibrosis, dermal fibrosis, vascular fibrosis as well as coronary artery disease and artherosclerosis.

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 preventing and/or treating fibrosis including all forms of AA and AL renal amyloidosis, idiopathic pulmonary fibrosis, drug induced pulmonary fibrosis, cystic fibrosis, peritoneal adhesion, pancreatic fibrosis, Uterine leiomyoma, renal interstitial fibrosis after allografted kidney transplantation, liver fibrosis, dermal fibrosis, vascular fibrosis as well as coronary artery disease and artherosclerosis.
Inhibition of c-Kit WT by AB molecules

FIGURE 1