Title: USE OF C-KIT INHIBITORS FOR TREATING RENAL DISEASES

Abstract: Provided are molecular circuits for the sustained expression of a gene of interest subsequent to a single application of stress. Generally, the circuits comprise (a) a first nucleic acid molecule that comprises a gene encoding a transcription factor and a first promoter or a combination promoter activatable by stress and by the transcription factor, wherein the first promoter or the combination promoter and the transcription factor gene are operably linked, and (b) a second nucleic acid molecule that comprises a gene of interest and a second promoter activatable by the transcription factor, wherein the second promoter and the gene of interest are operably linked.
Use of c-kit inhibitors for treating renal diseases

The present invention relates to a method for preventing or treating renal diseases and dysfunction comprising administering a compound capable of depleting mast cells 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.

The kidneys are the key organ for waste excretion and regulation of homeostasis, blood pH, electrolyte levels, as well as blood pressure. Renal failure or dysfunction is the cause of several diseases generally associated with hyper or hypotension. Renal diseases include acute nephritic syndrome, the nephrotic syndrome, progressive glomerulonephritis, asymptomatic hematuria and proteinuria, acute renal failure, urinary tract infection, and nephrolithiasis.

Acute nephritic syndrome is the result of inflammation of the internal structures of the kidney, caused by an immune response triggered most of the time by infection inflammation. Inflammation disrupts the functioning of the glomerulus, which controls filtering and excretion. Inefficient glomerular functioning results in the loss of blood and protein in the urine and the accumulation of excess fluid in the body. This disease is linked to hypertension, interstitial inflammation and may lead to acute renal failure. Corticosteroids or other anti-inflammatory medications may be used to reduce inflammation. Chronic glomerulonephritis is a progressive destruction of the glomeruli due to unexplained immune triggered inflammation. Corticosteroids and immunosuppressives are currently used for treating this renal disease.
It is now thought that interstitial inflammation and fibrosis results from the production of cytokines (IL-1, TNF-α...) in glomerulus. Chemokines are also found in tissue and are likely to promote cellular infiltration. Infiltrated monocyte and T lymphocyte secrete new cytokines that act on tubular epithelial cells and infiltrated cells, further participating in the inflammation process. Mast cells (MCs) have also been implicated in the pathogenesis of atherosclerosis and tissue fibrosis. However, the role of MC in the development of renal fibrosis has not been fully elucidated. In addition, the relation between mast cells and inflammation in renal diseases, and in particular glomerulonephritis, has been overlooked. Stem cell factor (SCF; the ligand for MC e-kit receptor) is thought to attract and activate MCs. A large number of MCs were detected in the renal interstitium of the diseased kidneys. Immunostainable SCF was detected in tubular as well as interstitial cells. MC infiltration was significantly higher in glomerulonephritis (16.9 +/- 10.2 cells/field) compared with controls (2.8 +/- 2.1 cells/field, P = 0.03). MCs as an infiltrating hematopoietic cell and its growth factor (SCF) seem to be up-regulated in glomerulonephritis, and may play a role in the development of renal fibrosis. (El-Koraie AF, Baddour NM, Adam AG, El Kashef EH, El Nahas AM. Role of stem cell factor and mast cells in the progression of chronic glomerulonephritides. Kidney Int. 2001 Jul;60(1):375-7).

Renal interstitial fibrosis is the final common pathway leading to end-stage renal disease in various nephropathies including renal amyloidosis. Toth and al. compared the distribution of MCs in renal biopsies from 30 patients with AA type renal amyloidosis and 20 control cases. Results indicate that MCs constitute an integral part of the overall inflammatory process and play a crucial role in interstitial fibrosis in renal amyloidosis. (Toth T, Toth-Jakatics R, Jimi S, Takebayashi S. Increased density of interstitial mast cells in amyloid A renal amyloidosis. Mod Pathol. 2000 Sep;13(9):1020-8.) However,
the role of mast cells (MCs) in the fibrotic process of renal amyloidosis is not fully understood.

The distribution of MC was also compared in renal biopsies from 50 patients with different stages of rapidly progressive GN (RPGN) and in 20 control samples. The immunoreactivity of renal MC with anti-tryptase and anti-chymase antibodies was studied. MC were rarely found in control samples. In contrast, samples showing crescentic GN contained numerous tryptase-positive MC (MC(T)) (43.7+/−4.65 versus 7.14+/−1.3/mm2) and fewer tryptase- and chymase-positive MC (MC(TC)) (13.8+/−1.86 versus 1.89+/−0.86/mm2) in the renal interstitium but never in the glomerulus. There was also a significant correlation between the number of MC(T) and the relative interstitial area. The number of MC(TC) was well correlated with the fractional area of alpha-SMA-positive interstitium (r = 0.749) and the percentage of the interstitial fibrotic area (r = 0.598). The density of MC(TC) was higher (1.4-fold) in advanced forms of GN associated with fibrocellular crescents and interstitial fibrosis. These results show the potential involvement of MC in the fibroproliferative process in the renal interstitium of patients with RPGN. The results indicate that these cells constitute part of the overall inflammatory cell accumulation in RPGN. (Toth T, Toth-Jaktics R, Jimi S, Ihara M, Urata H, Takebayashi S. Mast cells in rapidly progressive glomerulonephritis. J Am Soc Nephrol. 1999 Jul;10(7):1498-505.), but their exact role has not been determined as of today.

We propose here that mast cells are central in the renal inflammation process leading to interstitial inflammation and fibrosis. 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). Mast cells act as an infiltrating hematopoietic cell and its growth factor (SCF) is up-regulated in glomerulonephritis. MC also 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 leukotrienes), 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. When activated, these factors are secreted and participate in the development of fibrotic conditions of the kidneys. Renal fibrosis is closely linked with a chronic inflammatory cell infiltrate within the interstitium, but it is the first time that a potential role for mast cells in this process is proposed. Here, the numbers of mast cells in normal and fibrotic kidneys with various pathologies were investigated. An increased number of mast cells is a consistent feature of renal fibrosis, whatever the underlying pathology, and the number of mast cells correlates with the extent of interstitial fibrosis. This shows that mast cells play a pathogenetic role in the fibrotic process and are are central players involved in renal diseases.

In addition, we have discovered that c-kit inhibitors could be a new route for preventing or treating renal diseases which consist of destroying mast cells playing a role in renal deterioration. It has been found that selective and potent c-kit inhibitors are especially suited to reach this goal.

**Description**

The present invention relates to a method for treating and/or preventing or delaying the onset of renal diseases and dysfunction 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 preventing or treating renal 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, seleoindoles, selenides, tricyclic polyhydroxyl compounds and benzylphosphonic acid compounds.


So, preferably, the invention relates to a method for preventing or treating renal diseases 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:
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 preventing or treating renal diseases comprising the administration of an effective amount of the compound known in the art as CGP57148B:

4-(4-méthylpipérazine-1-ylméthyl)-N-[4-méthyl-3-(4-pyridine-3-yl)pyrimidine-2 ylamino]phényl]-benzamide corresponding to the following formula:
The preparation of this compound is described in example 21 of EP 564 409 and the β-form, which is particularly useful is described in WO 99/03854.

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

![Diagram of molecular structure]

**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, 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;

(iv) a heteroaryl group defined as a pyridyl, pyrimidiny1, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrroly1, 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 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, C₁₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₆alkylamino, di(C₁₆alkyl)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, thiencyl, 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, C₁₆alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, C₁₆alkylamino, di(C₁₆alkyl)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, C1₆alkyloxy, amino, C₁₆alkylamino, di(C₁₆alkyl)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 alkyl\(^1\), aryl\(^1\) or heteroaryl\(^1\).

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

\[
\begin{array}{c}
\text{R6} \\
\text{R4} \\
\text{R2} \\
\text{R1}
\end{array}
\]

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:

CH\(_2\), CH\(_2\)-CO, CH\(_2\)-CO-CH\(_2\), CH\(_2\)COO, CH\(_2\)-CH\(_2\)-CO, CH\(_2\)-CH\(_2\)-COO, CH\(_2\)-NH, CH\(_2\)-CH\(_2\)-NH, CH\(_2\)-NH-CH\(_2\) or CH\(_2\)-NH-CO or CH\(_2\)-CO-NH

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

CO-CH\(_2\), COO-CH\(_2\), CO-CH\(_2\)-CH\(_2\), CO-NH, or CO-NH-CH\(_2\)
as well as O-CH\(_2\)

It will also be understood that NH in B or B' can also be NCH\(_3\)

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 NCH\(_3\).

In the above formula, the following combinations are contemplated:
- R6 is (iv), R4 is H or CH\(_3\), 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 (iv), R4 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 alkyl\(^1\).
In the above combination, R1 can be an aryl\(^1\).
In the above combination, R1 can be an heteroaryl\(^1\).

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:

![Chemical Structure](image)

**FORMULA IV**

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;

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-thiazoly, 4-thiazoly, 5-thiazoly, 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 R² 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;

- SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or a -CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in a) and b) above, the invention is directed to N-Aminoalkyl-N'-thiazol-2-yl-benzene-1,3-diamine compounds of the following formula IVbis:
wherein Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms; 
wherein Z represents an aryl or heteroaryl group, optionally substituted at one or more 
ing 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 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 an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an OSO₂R, 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 NR\textsubscript{a}OSO\textsubscript{2}R\textsubscript{b}, where Ra and 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; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

R\textsuperscript{2} is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R\textsuperscript{3} is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R\textsuperscript{4} is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R\textsuperscript{5} is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R\textsuperscript{5} 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 R² 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:

\[
\text{FORMULA V}
\]

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

\( R^2 \) is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

\( R^3 \) 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.

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:

\[
\begin{align*}
\text{CN} & \quad \text{CN} \\
p & \quad q
\end{align*}
\]

In one particular embodiment, \( \text{R}_1 \) in formula III and IV, \( \text{X} \) in formula V and \( \text{Z} \) in formula IVbis can be:

\[
\begin{align*}
\text{Ri} & \quad \text{Rj} \\
\text{Rk} & \quad \text{Rl} \\
\text{Rm} & \quad \text{Rn}
\end{align*}
\]

wherein \( \text{Ri}, \text{Rj}, \text{Rk}, \text{Rl}, \text{Rm}, \text{Rn}, \text{Ro}, \) and \( \text{Rp} \) are independently chosen from:

- \( \text{H} \), 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'', NROSOR', 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, Ri, 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, Ri, Rm
is H.

Thus, the invention contemplates:

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

6- A compound of formula III or IV as depicted above wherein R² and/or R³ and/or R⁵ is H, R⁴ is a methyl group and R⁶ is a 3-pyridyl group.

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.

R⁴ is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluromethyl 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-thiényl, 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
Cyclohexane-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide
5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl-carbamoyl]-pentanoic acid ethyl ester
1-Methyl-cyclohexane-carboxylic 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:

```
\[
\begin{array}{c}
\text{R6} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{R4} \\
\text{R5} \\
\text{O} \\
\text{Ra} \\
\text{Rb}
\end{array}
\]
```

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

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.

**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-(4-trifluoromethyl-phenyl)-urea
1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea
4-[3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido]-benzoic acid ethyl ester
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea
1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea
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
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

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

10 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
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]-benzamide

15 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-trifluoromethylbenzamide

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
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

30 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
5 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
10 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide
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
15 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
20 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide
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
25 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]-
30 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 \textit{2-aminoaryloxazoles of formula X}:

![Diagram of the formula X]

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

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

- halogen (selected from I, F, Cl or Br);
- an alkyl\(^1\) group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- 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, 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) 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

(vii) 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.

25

X is:

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

or:

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

i) an alkyl\textsuperscript{1} group, CF3 or

ii) an aryl\textsuperscript{1}, heteroaryl\textsuperscript{1} 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:

\[
\begin{array}{c}
\text{N} \\
\text{R6} \\
\text{R7} \\
\text{O} \\
\text{N} \\
\text{R3} \\
\text{R4} \\
\text{R2} \\
\text{R1} \\
\text{Y} \\
\text{Z}
\end{array}
\]

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

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

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

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$^1$ or aryl$^1$ or heteroaryl$^1$, optionally substituted by a pendant basic nitrogen functionality, for example:

or a compound of formula XI-1:

FORMULA XI-1

wherein Ra, Rb are independently chosen from H or alkyl$^1$ or aryl$^1$ or heteroaryl$^1$, 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 aryl1 group, aryl1 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 alkyl1 group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl\textsuperscript{1}, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl\textsuperscript{1}, N(alkyl\textsuperscript{1})(alkyl\textsuperscript{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 NHSO\textsubscript{2}-R or NHSO\textsubscript{2}NH-R or CO-R or COO-R or CONH-R or SO\textsubscript{2}-R or SO\textsubscript{2}NH-R wherein R corresponds to hydrogen, alkyl\textsuperscript{1}, aryl or heteroaryl, for example

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure1}
\caption{Chemical structures}
\end{figure}

or a compound of formula XI-3:

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure2}
\caption{Chemical structures}
\end{figure}

**FORMULA XI-3**

wherein R\textsubscript{5} = H and R is independently alkyl\textsuperscript{1}, aryl\textsuperscript{1} or heteroaryl\textsuperscript{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
m.p.

5 4-Methyl-N1-(5-phenyl-oxazol-2-yl)-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
4-Methyl-N1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-
diamine
N1-Benzooxazol-2-yl-4-methyl-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
N-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-C-phenyl-methanesulfonamide

10 N-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-acetamide
2-Cyano-N-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-acetamide
2-Ethoxy-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-acetamide
3-Methoxy-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-propionamide
1-(4-Cyano-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea

15 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
1-(2-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
1-[4-Methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea
1-(4-Chloro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-urea
1-[4-Methyl-3-(5-phenyl-oxazol-2-ylamino)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea

20 1-(4-Cyano-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-thiourea
1-(4-Cyano-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-thiourea
(2-[2-Methyl-5-[3-(4-trifluoromethyl-phenyl)-ureido]-phenylamino]-oxazol-5-yl)-acetic acid
ethyl ester
1-Benzyl-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-thiourea

25 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-
benzamide
3-Dimethylamino-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-benzamide
3-Bromo-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-benzamide
N-[4-Methoxy-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide
4-(3-Dimethylamino-propylamino)-N-[4-methyl-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

N-[4-Fluoro-3-(5-pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

1H-Indole-6-carboxylic acid [4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amide

3-Isopropoxy-N-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-benzamide

N-[4-Methyl-3-(5-pyridin-2-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

3,5-Dimethoxy-N-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-benzamide

N-[3-(5-Pyridin-3-yl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

N-[4-Methyl-3-(5-phenyl-oxazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

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-Isobutoxycarbonylamino-2-methyl-phenyl)-(5-pyridin-3-yl-oxazol-2-yl)-carbamic acid isobutyl ester

[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester

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

**Process for manufacturing a compound of formula III depicted above.**

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

\[ \text{11 a: } X = \text{NH-R1} \]
\[ \text{11 b: } X = \text{NH2} \]
\[ \text{11 c: } X = \text{NH-PG} \]
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.

\[
\begin{align*}
\text{R6} & \quad \text{R4} & \quad \text{R3} & \quad \text{R2} \\
\text{R7} & \quad \text{R5} & \quad \text{X} \\
\end{align*}
\]

12 a: \( X = \text{NH-R1} \)
12 b: \( X = \text{NH2} \)
12 c: \( X = \text{NH-PG} \)
12 d: \( X = \text{NO}_2 \)

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:

\[
\text{12b + "R1" → III}
\]

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 renal diseases as referred herein includes the following potential therapeutic applications: all forms of AA and AL renal amyloidosis, renal interstitial fibrosis after allografted kidney transplantation, renal fibrosis, glomerulonephritis, nephropathy, Balkan nephropathy, acute interstitial nephritis, lupus nephritis, inflammatory renal diseases, lupus nephropathy, ANCA-associated nephropathy, IgA nephropathy, glomerulopathy.

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 and/or preventing or delaying the onset of renal diseases and dysfunction 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;

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 or treating renal diseases including all forms of AA and AL renal amyloidosis, renal interstitial fibrosis after allografted kidney transplantation, renal fibrosis, glomerulonephritis, nephropathy, Balkan nephropathy, acute interstitial nephritis, lupus nephritis, inflammatory renal diseases, lupus nephropathy, ANCA-associated nephropathy, IgA nephropathy, glomerulopathy.
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>
<thead>
<tr>
<th>Enzyme / Cell line</th>
<th>IC50 [μM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro enzymatic assay on purified kinases</td>
<td></td>
</tr>
<tr>
<td>c-Kit</td>
<td>0.01</td>
</tr>
<tr>
<td>PDGF-beta</td>
<td>0.49</td>
</tr>
<tr>
<td>ABL1</td>
<td>5.7</td>
</tr>
<tr>
<td>VEGFR1</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>EGFR</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>FGFR1</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>FLT3</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>JAK2</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>AKT1</td>
<td>57</td>
</tr>
<tr>
<td>PKC-alpha</td>
<td>100</td>
</tr>
<tr>
<td>SRC</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>IGF1R</td>
<td>IC50 &gt; 100</td>
</tr>
<tr>
<td>PIM1</td>
<td>19</td>
</tr>
</tbody>
</table>

In vitro.

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 and/or preventing or delaying the onset of renal diseases and dysfunction 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 renal diseases 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-aminoaryloxazoles,
   - 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:
wherein

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

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

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

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

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

(iv) a heteroaryl¹ group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl,
thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, triazolyl,
tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as

- halogen (selected from F, Cl, Br or I);
- 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 SO\(_2\)R\(^8\) 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_{1-6}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 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.

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_{1-6}alkyloxy, amino, 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.
alkylamino, di(C₆-alkyl)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, NH₂SO₂, NH₂SO₂NH, 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.

6. A method according to claim 5, wherein said c-kit inhibitor is selected from compounds of formula "\[\]".
FORMULA V

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

\( R^2 \) is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

\( R^3 \) 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.

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

![Formula X](image_url)

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

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

R₅ is one of the following:
(i) hydrogen, or
(ii) a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality, or
(iii) CO-R₈ or COOR₈ or CONHR₈ or SO₂R₈ wherein R₈ may be

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

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

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

R⁶ and R⁷ each independently are selected from:

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

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

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

- halogen (selected from I, F, Cl or Br);
- an alkyl$^1$ group;
- a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant
  basic nitrogen functionality;
- 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, 
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;
- 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, or NH-aryl, or O-heteroaryl or NH-heteroaryl group
(vi) 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, 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, aryl or heteroaryl.

X is:

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

or:

-CO-NR9R10, wherein R9 and/or R10 are hydrogen or:
  i) an alkyl group, CF3 or
  ii) an aryl, heteroaryl 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-yilméthyl)-N-[4-méthyl-3-(4-pyridine-3-y1)pyrimidine-2 ylamino]phényl]-benzamide.

10. A method for treating and/or preventing or delaying the onset of renal diseases and dysfunction 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 patients suffering from renal diseases selected from all forms of AA and AL renal amyloidosis, renal interstitial
fibrosis after allografted kidney transplantation, renal fibrosis, glomerulonephritis, nephropathy, Balkan nephropathy, acute interstitial nephritis, lupus nephritis, inflammatory renal diseases, lupus nephropathy, ANCA-associated nephropathy, IgA nephropathy, and glomerulopathy.

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 or treating renal diseases including all forms of AA and AL renal amyloidosis, renal interstitial fibrosis after allografted kidney transplantation, renal fibrosis, glomerulonephritis, nephropathy, Balkan nephropathy, acute interstitial nephritis, lupus nephritis, inflammatory renal diseases, lupus nephropathy, ANCA-associated nephropathy, IgA nephropathy, glomerulopathy.
Inhibition of c-Kit WT by AB molecules

FIGURE 1