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(54) **Title:** AMINOARYL SUBSTITUTED FIVE-MEMBERED RING HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF DISEASES

(57) **Abstract:** The present invention relates to novel compounds selected from aminoaryl five-membered ring heterocycles that selectively modulate, regulate and/or inhibit signal transduction mediated by certain native and/or mutant tyrosine kinases implicated in a variety of human and animal diseases such as cell proliferative, metabolic, allergic, and degenerative disorders.

WO 2006/064375 A2

Aminoaryl substituted five-membered ring heterocyclic compounds for the treatment of diseases

The present invention relates to novel compounds selected from aminoaryl five-membered ring heterocycles that selectively modulate, regulate, and/or inhibit signal transduction mediated by native and/or mutant tyrosine kinases implicated in a variety of human and animal diseases such as cell proliferative, metabolic, allergic, inflammatory and degenerative disorders.

Tyrosine kinases are receptor type or non-receptor type proteins, which transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration as well as inflammation.

As of today, there are about 58 known receptor tyrosine kinases. Included are the well-known VEGF receptors (Kim et al., Nature 362, pp. 841-844, 1993), PDGF receptors, c-kit, Flt-3 and the FLK family. These receptors can transmit signals to other tyrosine kinases including Src, Raf, Frk, Btk, Csk, Abl, Fes/Fps, Fak, Jak, Ack, etc.

Among tyrosine kinase receptors, some are of special interest and have been shown to be directly or indirectly implicated in numerous pathologies for which the Applicant filed WO 03/004007, WO 03/004006, WO 03/003006, WO 03/003004, WO 03/002114, WO 03/002109, WO 03/002108, WO 03/002107, WO 03/002106, WO 03/002105, WO 03/039550, WO 03/035050, WO 03/035049, WO 03/0720090, WO 03/072106 and WO 2004/014903.

Many different compounds have been described as tyrosine kinase inhibitors, for example, bis monocyclic, bicyclic or heterocyclic aryl compounds (WO 92/20642), vinylene-azaindole derivatives (WO 94/14808), 1-cyclopropyl-4-pyridyl-quinolones

(US 5,330,992), styryl compounds (US 5,217,999), styryl-substituted pyridyl compounds (US 5,302,606), selenoindoles and selenides (WO 94/03427), tricyclic polyhydroxylic compounds (WO 92/21660), benzylphosphonic acid compounds (WO 91/15495), pyrimidine derivatives (US 5,521,184 and WO 99/03854), indolinone derivatives and pyrrole-substituted indolinones (US 5,792,783, EP 934 931, US 5,834,504, US 5,883,116, US 5,883,113, US 5, 886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, US 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520 722, US 3,772,295 and US 4,343,940) and aryl and heteroaryl quinazoline (US 5,721,237, US 5,714,493, US 5,710,158 and WO 95/15758).

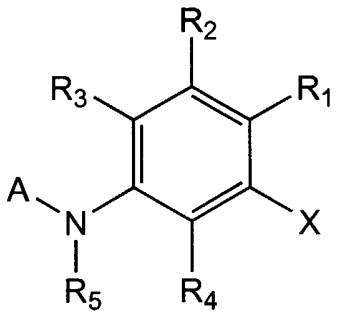
There are hundreds of tyrosine kinases in mammalian cells that are more or less proned to be modulated by the compounds cited above. The problem is that a tyrosine kinase inhibitor has to be very specific to one or very few kinases to avoid toxicity and side effects on the long run. None of these prior art tyrosine kinase inhibitors provides a solution for this problem.

In connection with the present invention, we have found that compounds corresponding to the **aminoaryl five-membered ring heterocycles** are potent and selective inhibitors of tyrosine kinases. These compounds are good candidates for treating diseases such as autoimmunes diseases, inflammatory diseases, as well as cancers.

Description

Therefore, the present invention relates to compounds belonging to the **aminoaryl five-membered ring heterocycles**. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase, for example VEGF receptors, PDGF receptors, c-kit, Flt-3 and the FLK family, Src, Raf, Frk, Btk, Csk, Abl, Fes/Fps, Fak, Jak, Ack ; and mutant forms thereof.

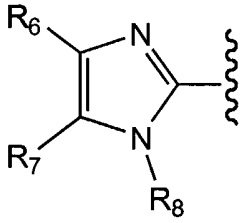
In a first embodiment, the invention is aimed at compounds of formula **I**, which may represent either free base forms of the substances or pharmaceutically acceptable salts thereof:



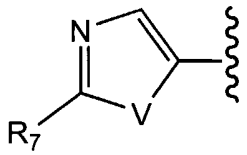
FORMULA I

Wherein A is selected from the group consisting of:

- Imidazole (formula I-1)

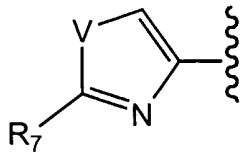


- 5-Aminothiazole/oxazole (formula I-2)



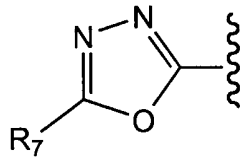
V = S or O

- 4-Aminothiazole/oxazole (formula I-3)

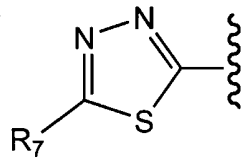


V = S or O

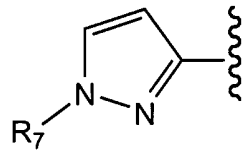
- Oxadiazole (formula I-4)



- Thiadiazole (formula I-5)



- Pyrazole (formula I-6)



Substituents R1 – R8 and X in Formula I 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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of

an amino group; as well as trifluoromethyl, C_{1-6}alkyloxy, amino, C_{1-6}alkylamino, di(C_{1-6}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 an amino group.

R5 and R8 are 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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of an amino group, or

(iii) CO-R or COOR or CONHR or SO2R wherein R may be

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

- a heteroaryl group such as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, -heterocycleyl, pyrazolyl, pyrrolyl, furanyl, -heterocycleyl, is-

heterocycleyl, triazolyl, tetrazolyl, indolyl, benz-heterocycle, 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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of an amino group; 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 an amino group; 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 an amino group.

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, or from 2 or 3 to 10 carbon atoms, (for example methyl, ethyl, propyl, butyl, pentyl, hexyl...) and optionally substituted with one or more hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of an amino group); 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, or from 2 or 3 to 10 carbon atoms, (for example methyl, ethyl, propyl, butyl, pentyl, hexyl...) 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 an amino group ; as well as a cycloalkyl or aryl[1] or heteroaryl[1] group optionally substituted by an amino group,

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 an amino group;
- 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 an amino group;
- 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, -heterocycleyl, pyrazolyl, pyrrolyl, furanyl, -heterocycleyl, is-heterocycleyl , triazolyl, tetrazolyl, indolyl, benz-heterocycle, 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 an amino group,
- 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 an amino group;
- 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 hydrogern, alkyl^1, or

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

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

(vi) NHCO-R or NHCOO-R or NHCONH-R or NHSO2-R or NHSO2NH-R or CO-R or COO-R or CONH-R or SO2-R or SO2NH-R wherein R corresponds to hydrogen, alkyl[1], aryl or heteroaryl.

Substituent **X** is:

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

i) an alkyl[1] group, CF3 or

ii) an aryl[1], heteroaryl[1] or cycloalkyl group optionally substituted by a an amino group, or

iii) a CO-R, COO-R, CON-RR'or SO2-R, where R and R' are a hydrogen, alkyl[1], aryl[1] or heteroaryl[1], optionally substituted by an amino group;

or:

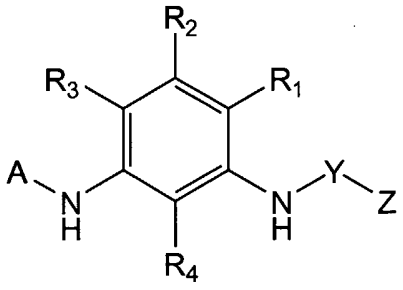
-CO-NR9R10, wherein R9 and / or R10 are hydrogen or:

i) an alkyl[1] group, CF3 or

ii) an aryl[1], heteroaryl[1] or cycloalkyl group optionally substituted by a an amino group, or

X may also be Alkyl[1].

Among the particular compounds of formula **I**, the invention is directed to heterocycle **A**-yl-benzene-1,3-diamine compounds of the following formula **II**:

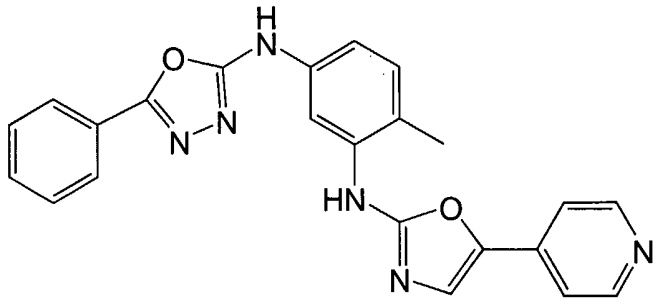


FORMULA II

Y and Z represents an hydrogen, an aryl[1] or a heteroaryl[1] group, optionally substituted by an amino group. A, R1, R2, R3 and R4 have the meaning as depicted above.

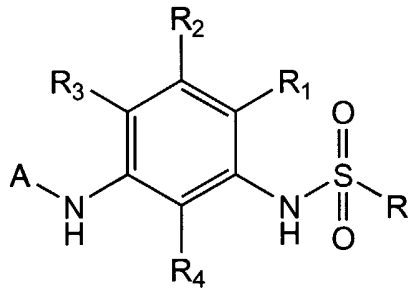
Examples:

00 1: 4-Methyl-*N*1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine



m.p. > 260°C

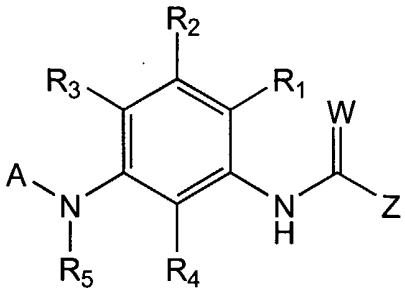
Among the compounds of formula I, the invention is particularly embodied by the compounds wherein R5 = H, X is NHSO2R group, R is independently alkyl[1], aryl[1] or heteroaryl[1] corresponding to the family [3-(-heterocycle A-ylamino)-phenyl]-sulfonamide and the following formula **III** :



FORMULA III

R represent an hydrogen, an alkyl[1], aryl[1] or a heteroaryl[1] group. A, R1, R2, R3, and R4 have the meaning as defined above in formula I.

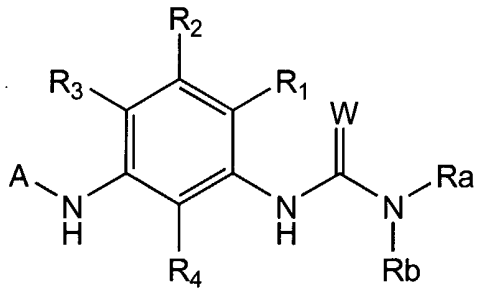
Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula **IV**:



FORMULA IV

Wherein W is selected from O, S and Z corresponds to H, alkyl[1], NRaRb, or OR wherein Ra and Rb and R are independently chosen from H or alkyl[1] or aryl[1] or heteroaryl[1], optionally substituted by an amino group. A, R1, R2, R3, R4 and R5 have the meaning described above for formula I.

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein R5 = H, W = O or S, Z is a NRaRb group, corresponding to the [3-(-heterocycle A-ylamino)-phenyl]-urea or the [3-(-heterocycle A-ylamino)-phenyl]-thiourea family and the following formula V :

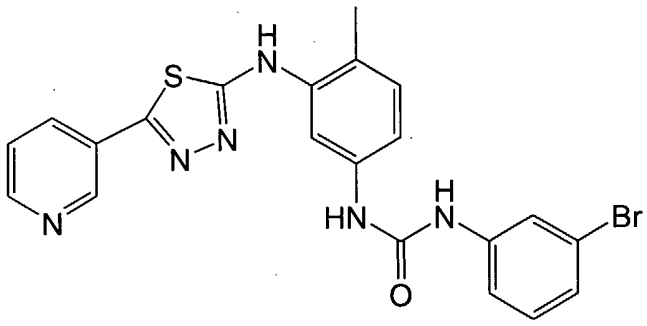


FORMULA V

wherein Ra, Rb are independently chosen from H or alkyl[1] or aryl[1] or heteroaryl[1], optionally substituted by an amino group. A, R1, R2, R3, R4 and W have the meaning described above.

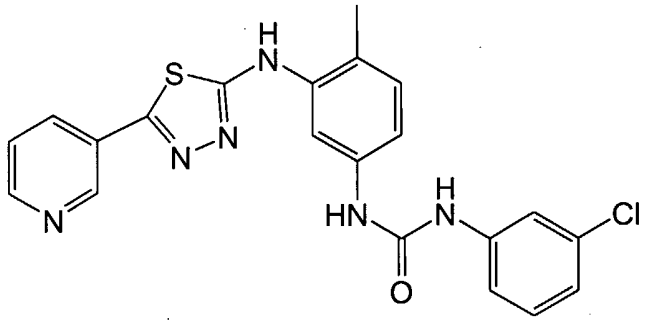
Examples:

002 : 1-(3-Bromo-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-ylamino)-phenyl]-urea



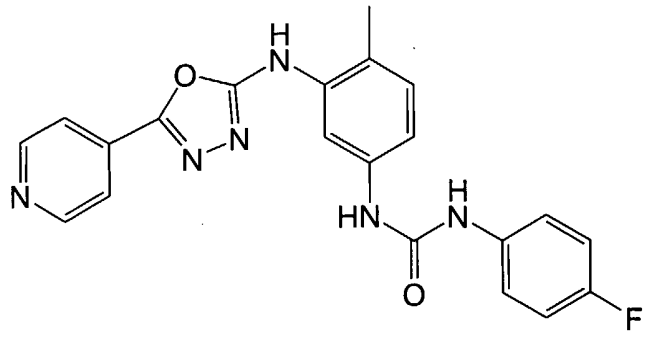
m.p. = 251°C

003 : 1-(3-Chloro-phenyl)-3-[4-methyl-3-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-ylamino) -phenyl]-urea



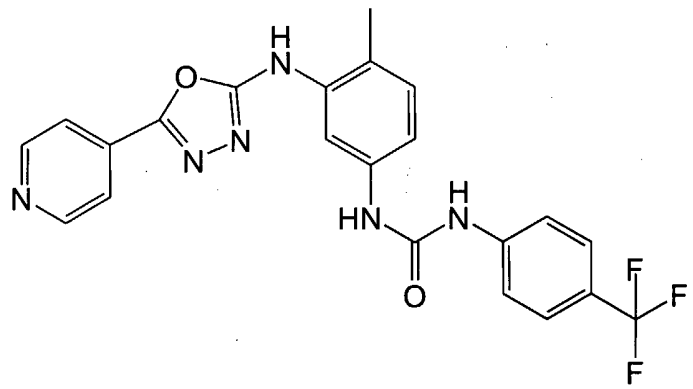
m.p. = 245°C

004 : 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-ylamino)-phenyl]-urea



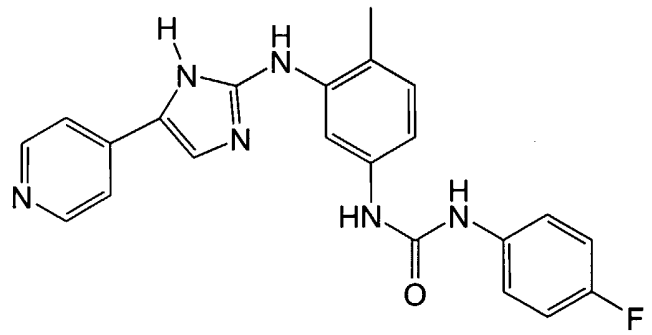
m.p. = 261°C

005 : 1-[4-Methyl-3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea



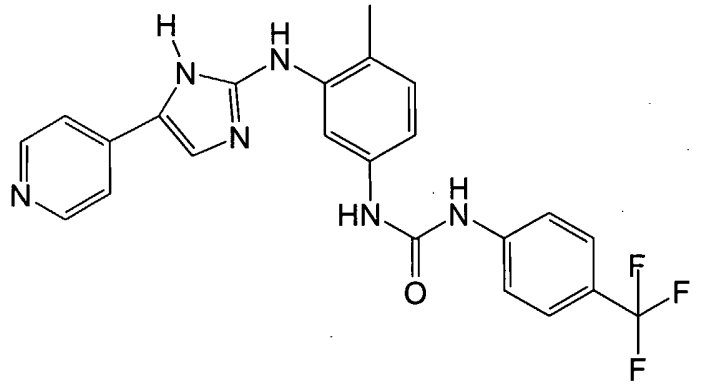
m.p. = 252°C

006 : 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-1H-imidazol-2-ylamino)-phenyl]-urea



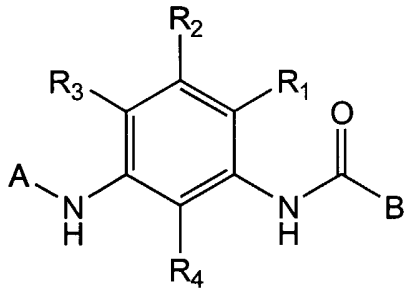
m.p. = 190°C

007 : 1-[4-Methyl-3-(5-pyridin-4-yl-1H-imidazol-2-ylamino)-phenyl]-3-(4-trifluoro methyl-phenyl)-urea



m.p. = 186°C

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein R5 = H, Y is an oxygen, corresponding to the N-[3-(-heterocycle A-ylamino)-phenyl]-amide family and the following formula VI :



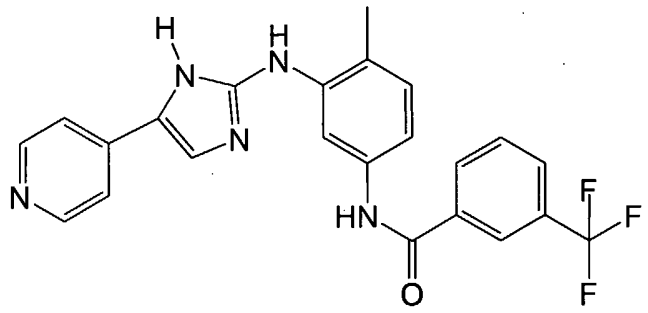
FORMULA VI

Wherein B is aryl[1] or heteroaryl[1] and

Wherein A, R1, R2, R3, R4, aryl[1], heteroaryl[1] have the meaning described on pages as defined in formula I.

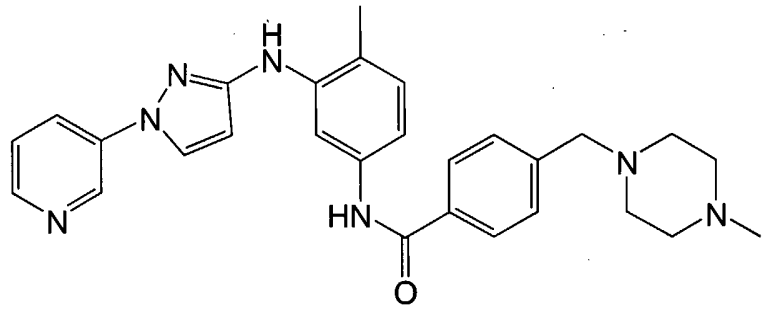
Examples:

008 : N-[4-Methyl-3-(5-pyridin-4-yl-1H-imidazol-2-ylamino)-phenyl]-3-trifluoro methyl-benzamide

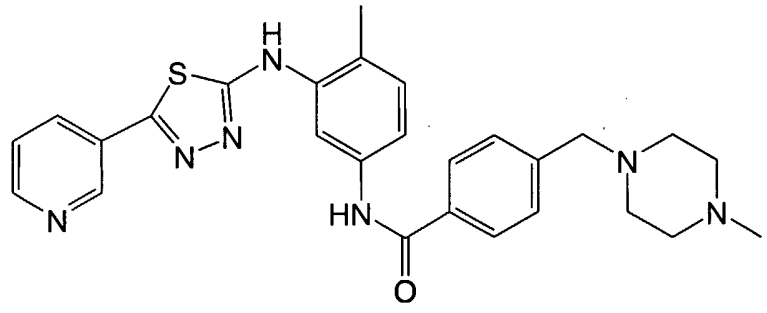


m.p. > 260°C

009 : 4-(4-Methyl-piperazin-1-ylmethyl)-*N*-[4-methyl-3-(1-pyridin-3-yl-1*H*-pyrazol-3-ylamino)-phenyl]-benzamide

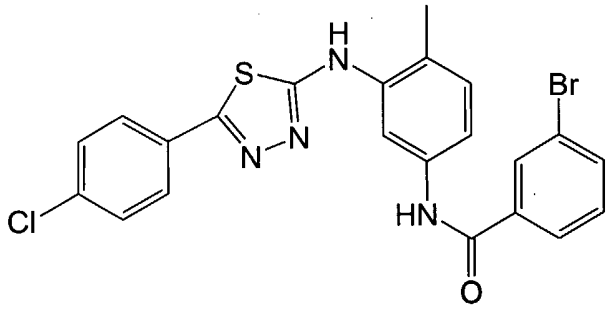


010 : 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(5-pyridin-3-yl-[1,3,4] thiadiazol-2-ylamino)-phenyl]-benzamide



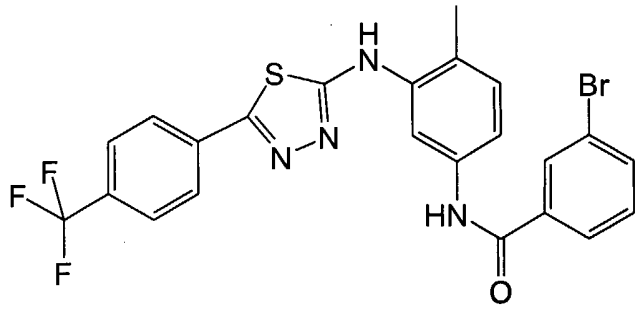
m.p. = 172°C

011 : 3-Bromo-N-{3-[5-(4-chloro-phenyl)-[1,3,4]thiadiazol-2-ylamino]-4-methyl-phenyl}-benzamide



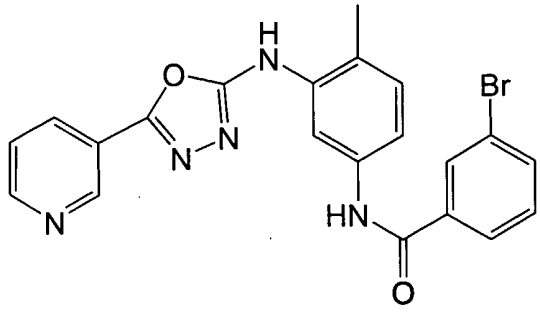
m.p. = 193°C

012 : 3-Bromo-N-{4-methyl-3-[5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-ylamino]-phenyl}-benzamide



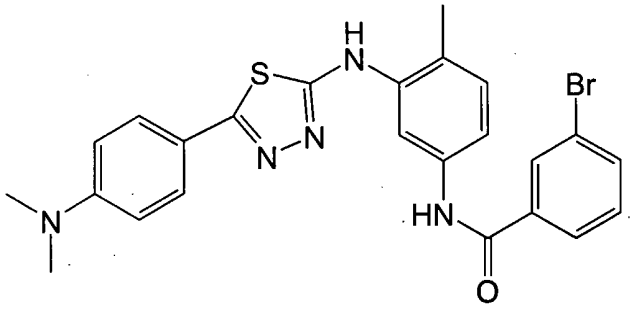
m.p. = 231°C

013 : 3-Bromo-N-[4-methyl-3-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylamino)-phenyl]-benzamide



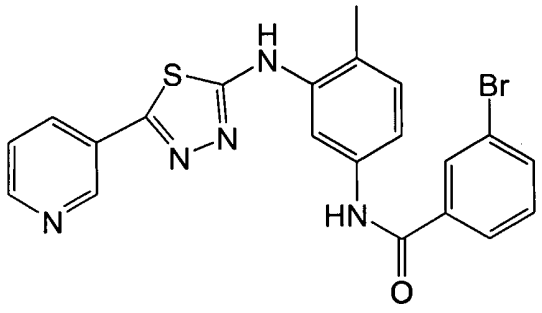
m.p. = 256°C

014 : 3-Bromo-N-{3-[5-(4-dimethylamino-phenyl)-[1,3,4]thiadiazol-2-ylamino]-4-methyl-phenyl}-benzamide



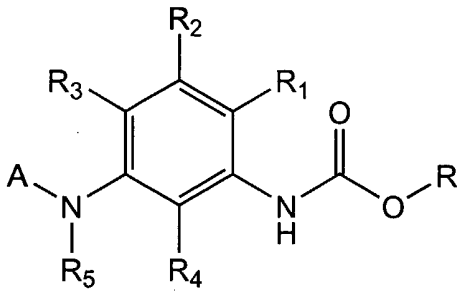
m.p. > 260°C

015 : 3-Bromo-N-[4-methyl-3-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-ylamino)-phenyl]-benzamide



m.p. = 242°C

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein Y = O and Z a OR group, corresponding to the family [3-(-heterocycle A-2-ylamino)-phenyl]-carbamate and the following formula VII.

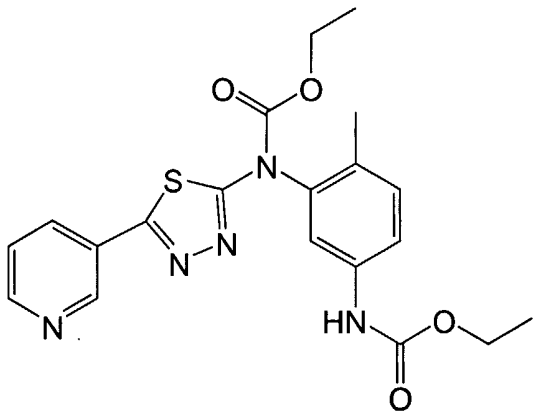


FORMULA VII

wherein R is independently alkyl[1], aryl[1] or heteroaryl[1]. A, R1, R2, R3, R4 and R5 have the meaning described above for formula I.

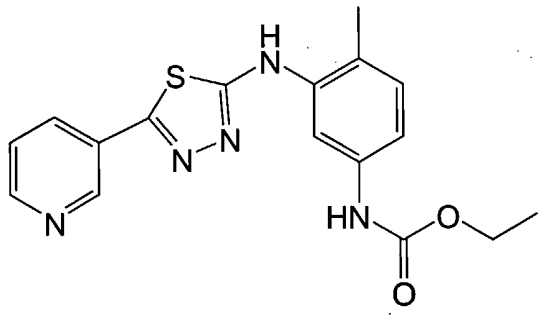
Examples:

016 : (5-Ethoxycarbonylamino-2-methyl-phenyl)-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-yl)-carbamic acid ethyl ester

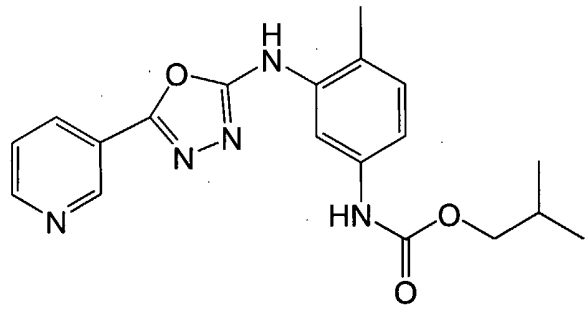


m.p. = 120-130°C

017 : [4-Methyl-3-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-ylamino)-phenyl]-carbamic acid ethyl ester

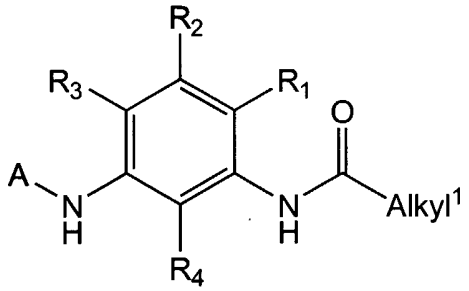


018 : [4-Methyl-3-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester



m.p. = 186°C

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein R5 = H, Y is an oxygen and Z an alkyl[1] group, corresponding to the family [3-(-heterocycle A-ylamino)-phenyl]-acetamide and the following formula VIII.

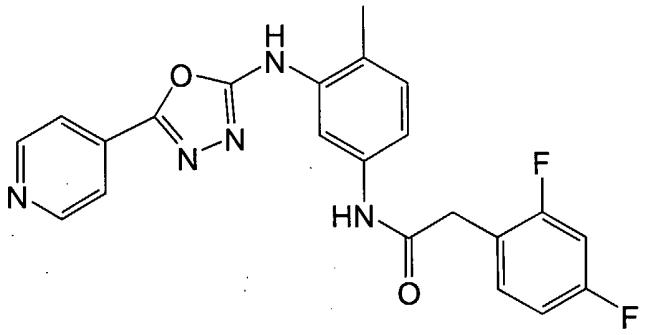


FORMULA VIII

A, R1, R2, R3, R4 and alkyl[1] have the meaning as defined above.

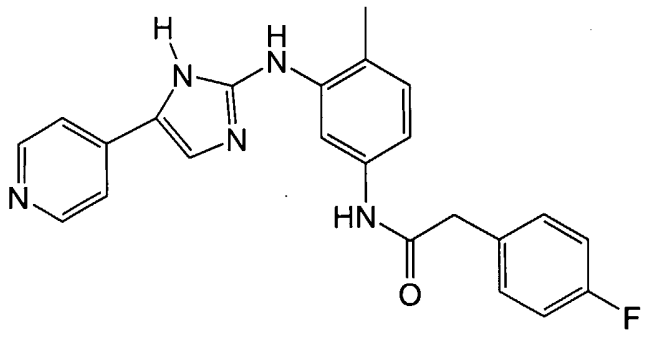
Examples:

019 : 2-(2,4-Difluoro-phenyl)-*N*-[4-methyl-3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl amino)-phenyl]-acetamide



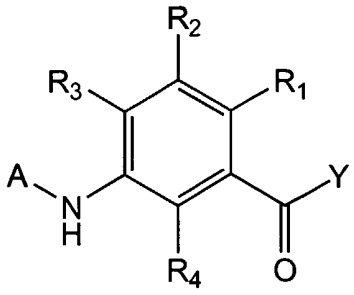
m.p. = 256°C

020 : 2-(4-Fluoro-phenyl)-N-[4-methyl-3-(5-pyridin-4-yl-1H-imidazol-2-ylamino)-phenyl]-acetamide



m.p. = 160°C

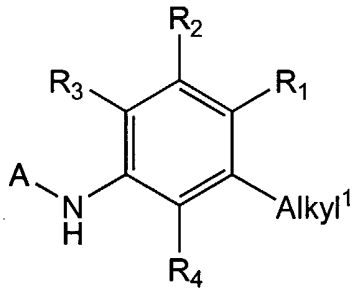
Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula IX :



FORMULA IX

Wherein Y is selected from NRaRb, NHNRaRb, alkyl[1], aryl[1], or OR wherein Ra, Rb and R are independently chosen from H or alkyl[1] or aryl[1] or heteroaryl[1], optionally substituted by an amino group. A, R1, R2, R3 and R4 have the meaning described above for formula I.

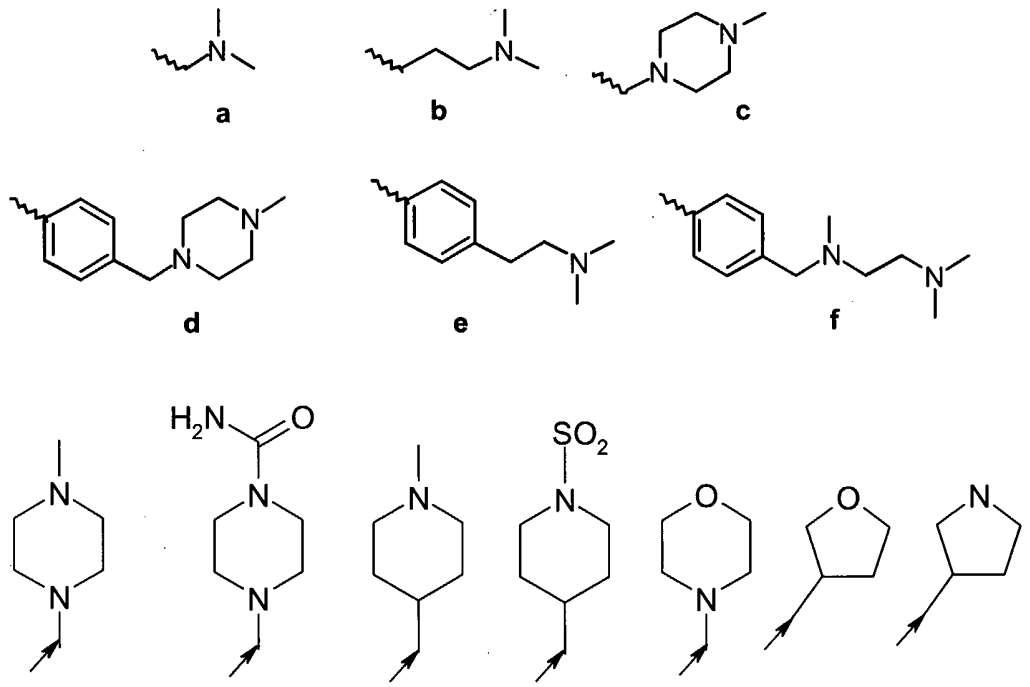
Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula X :



FORMULA X

Wherein alkyl[1], A, R1, R2, R3 and R4 have the meaning as defined for formula I above.

In the compounds described above of formula I to X, the optional substitution by an amino group may be represented for example by the structures **a** to **k and m** shown below, wherein the wavy line and the arrow line correspond to the point of attachment to core structure of formula **I-X**.



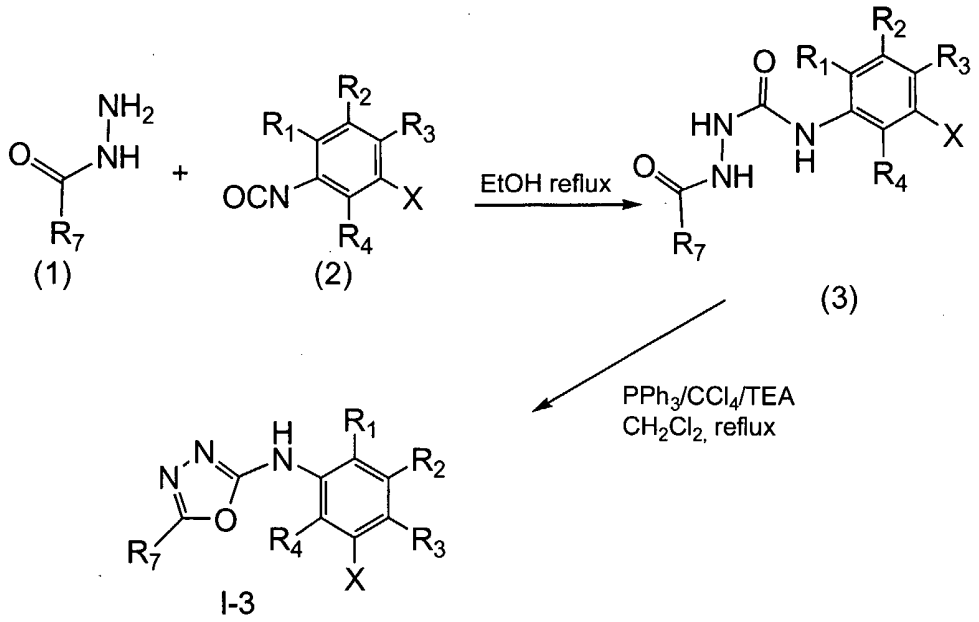
Also, for g to m the arrow may include a point of attachment to the core structure via a phenyl group. Group l above is an alternative encompassed herein.

For example, the amino group may be a saturated cyclic amino group which may be substituted by a group consisting of alkyl, alkoxycarbonyl, halogen, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carbamoyl, monoalkylcarbamoyl and dialkylcarbamoyl.

The compounds of the present invention are prepared according to procedures known to the skilled in the art. For example :

Condensation of the appropriate hydrazide (1) with isocyanate (2) in a solvent such as ethanol or dimethylformamide yields the carbonylhydrazide intermediate (3). Treatment of (3) with CCl_4, triphenylphosphine and a base such trimethylamine in the presence of a suitable solvent such as dichloromethane yield oxadiazole I-3.

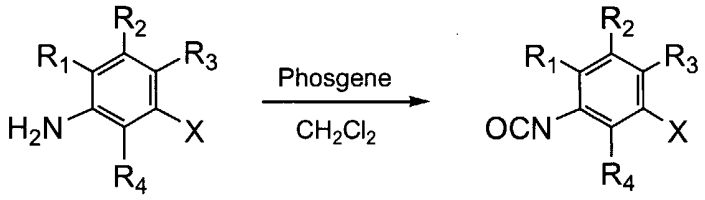
Scheme 1



Intermediate (2) are commercially available or can prepared by reaction of an appropriate amine (10) with a reagent like phosgene or triphosgene in a solvent such as dichloromethane.

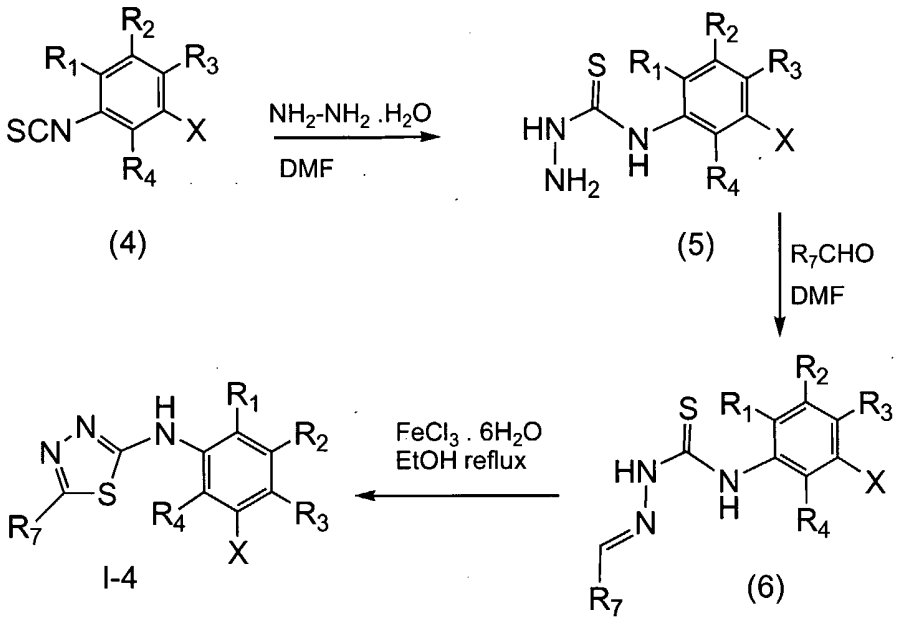
Intermediate (1) are commercially available or can prepared by reaction of an appropriate ester with hydrazine monohydrate in a solvent such as EtOH.

Scheme 2



Reaction of isothiocyanate (4) with hydrazine monohydrate in solvent such EtOH or DMF gives thiosemicarbazide (5). Condensation of (5) with an appropriate aldehyde in DMF yields the intermediate (6). Oxidative cyclization of Schiff's base (6) with iron (III) chloride with reflux in EtOH yields the thiadiazole I-4.

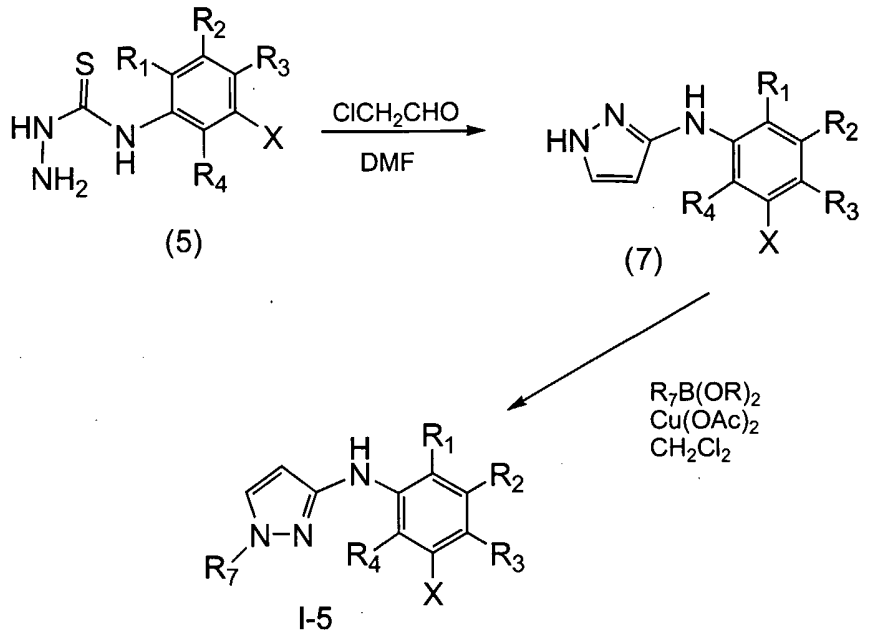
Scheme 3



Intermediate (4) are commercially available or can prepared by reaction of an appropriate amine (10) with a reagent like thiophosgene, 1,1'-thiocarbonyldiimidazole or 1,1'-thiocarbonyldi-2(1*H*)-pyridone in a solvent such as dichloromethane.

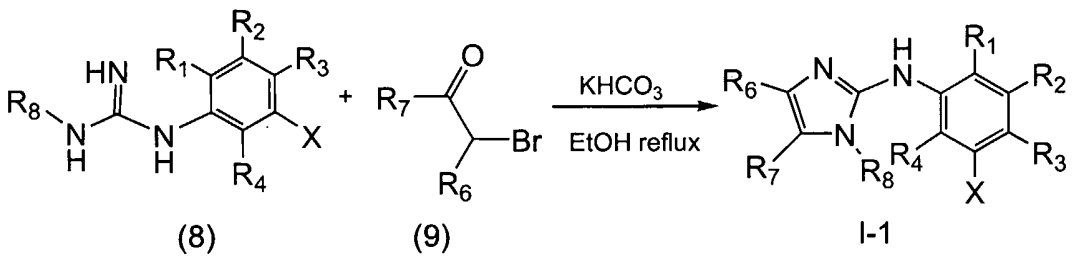
Reaction of intermediate (5) with the commercially chloroacetaldehyde in the presence of 4 equivalents of HCl (10*N*) in a solvent such EtOH or dioxane yields compound (7). Aminopyrazole (7) was coupled with an appropriate boronic acid in the presence of a suitable catalyst such as $Cu(OAc)_2$ in a solvent such dichloromethane to give the pyrazole I-5.

Scheme 4



Synthesis of imidazole I-1 was performed by condensation of guanidine (8) with an appropriate 2-halogenoacetopnenone (9) in the presence of a mineral base such $KHCO_3$ or $NaHCO_3$. Suitable solvent for such synthesis are, e.g., EtOH or DMF.

Scheme 5



Intermediate (8) are commercially available or can prepared by reaction of an appropriate amine (10) with a appropriate cyanamide in the presence of HCl. Meta-cresol is preferably employed such as solvent for this synthesis.

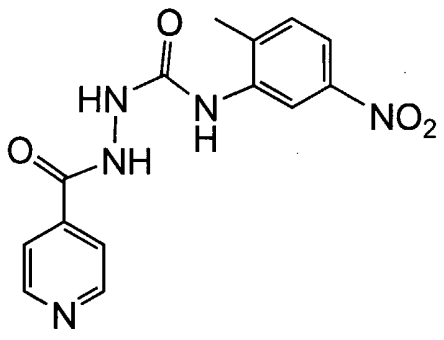
Some of intermediates and starting materials are known compounds and may be commertcially available or may be prepared according to art-known procedures.

The following example is intended to illustrate the present invention.

Example of Compound synthesis

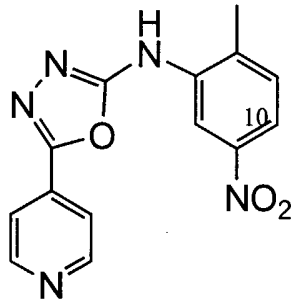
General: All chemicals used were commercial reagent grade products. Solvents were of anhydrous commercial grade and were used without further purification. Dichloromethane and dioxane were freshly distilled under a stream of argon before use. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Merck TLC plates, which were visualized under UV light. Multiplicities in ^{1}H NMR spectra are indicated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300 MHz Bruker spectrometer.

Preparation of *N'*-(Pyridine-4-carbonyl)-hydrazinecarboxylic acid 2-methyl-5-nitro-phenyl amide



A solution of 2-Isocyanato-1-methyl-4-nitro-benzene (1 g, 5.6 mmol) and Isonicotinic acid hydrazide (767 mg, 5.6 mmol) in EtOH (10 mL) was refluxed for 4h. After cooling, the formed precipitate was filtred off and recrystallized from ethyl alcohol to give 1.15 g of a white crystals (65%).

Preparation of (2-Methyl-5-nitro-phenyl)-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-amine

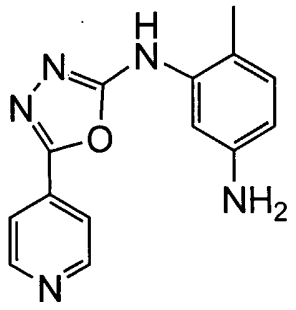


To a stirred solution of triphenylphosphine (1 g, 3.8 mmol) in CH_2Cl_2 (20 mL), *N'*-(Pyridine-4-carbonyl)-hydrazinecarboxylic acid 2-methyl-5-nitro-phenyl amide (1.05 g, 3.17 mmoL), triethylamine (0.66 mL, 4.76 mmoL) and CCl_4 (0.93 mL) were added under nitrogen at room temperature. The mixture was stirred at room temperature for 30 min., then refluxed for 6h. The precipitate was filtred off and recrystallized from EtOH to give 510 mg of a yellow crystals (54%).

m.p. = 251 °C

^{1}H NMR (DMSO-d^6) δ = 2.47 (s, 3H) ; 7.54 (d, J = 8.4 Hz, 1H) ; 7.83 (d, J = 6.0 Hz, 2H) ; 7.91 (dd, J = 8.4-2.1 Hz, 1H) ; 8.81 (d, J = 6.0 Hz, 2H) ; 8.94 (d, J = 2.1 Hz, 1H) ; 10.35 (br s, 1H).

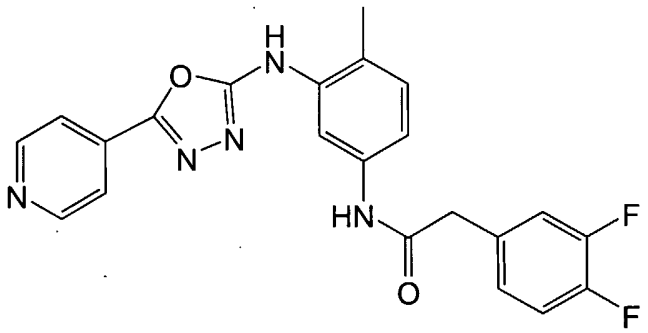
Preparation of 4-Methyl-*N*3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-benzene-1,3-diamine



To a solution of (2-Methyl-5-nitro-phenyl)-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-amine (400 mg, 1.28 mmol) in ethanol (15 mL) was added tin(II) chloride dihydrate (1.6 g, 6.4 mmol). The reaction mixture was heated under reflux for 3h. The mixture was then concentrated, saturated aqueous $NaHCO_3$ was added and the resultant suspension was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was silica gel column chromatographed (dichloromethane/ethanol : 97/3). 320 mg (94%) of 4-Methyl-*N*3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-benzene-1,3-diamine was obtained as pale yellow powder.

m.p. = 212°C

Preparation of 2-(3,4-Difluoro-phenyl)-*N*-[4-methyl-3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-ylamino)-phenyl]-acetamide



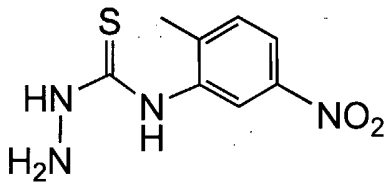
To a solution of 4-Methyl-*N*3-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-benzene-1,3-diamine (50 mg, 0.187 mmol) and (3,4-Difluoro-phenyl)-acetic acid (48 mg, 0.279

mmol) in DMF (4 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (55 mg, 0.333 mmol), 1-hydroxybenzotriazole (40 mg, 0.290 mmol) and triethylamine (0.046 ml, 0.355 mmol). The mixture was stirred at room temperature for 16h. After removal of the solvent, the residue was treated with saturated aqueous $NaHCO_3$ (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. 2-(3,4-Difluoro-phenyl)-*N*-[4-methyl-3-(5-pyridin-4-yl-[1,3,4]oxadiazol -2-ylamino)-phenyl]-acetamide was obtained after silica gel column chromatography (dichloromethane/ethanol : 98/2) (55 mg , 70%) as white solid.

m.p. = 256 °C

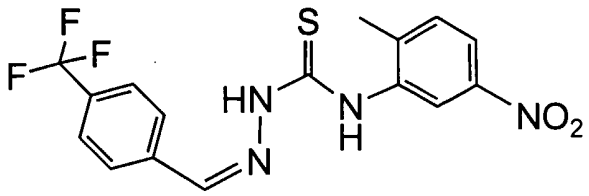
^{1}H NMR (DMSO-d^6) δ = 2.25 (s, 3H) ; 3.82 (s, 2H) ; 7.05-7.48 (m, 5H) ; 7.80 (d, J = 6.0 Hz, 2H) ; 8.04 (br s, 1H) ; 8.76 (d, J = 6.0 Hz, 2H) ; 9.88 (br s, 1H) ; 10.76 (br s, 1H).

Preparation of Hydrazinecarbothioic acid *N*-(2-methyl-5-nitro-phenyl)amide



A solution of 2-thioisocyanato-1-methyl-4-nitro-benzene (1 g, 5.0 mmol), hydrazine monohydrate (1.25 mL, 25.6 mmol) in DMF (10 mL) was stirred at room temperature for 2h. After removal of the solvent, the residue was treated with EtOH and the precipitate collected by filtration, washed with ice-cold ethanol and dried under *vacum* to give 1.05 g of a yellow solid (86%).

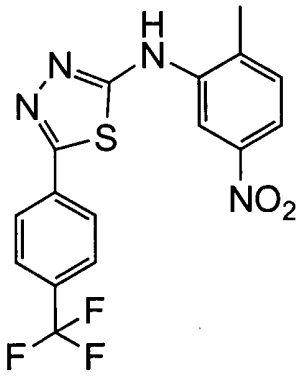
Preparation of *N'*-(4-Trifluoromethyl-benzylidene)-hydrazinecarbothioic acid *N*-(2-methyl-5-nitro-phenyl) amide



To a solution of 475 mg (2.10 mmol) of hydrazinecarbothioic acid *N*-(2-methyl-5-nitro-phenyl) amide in DMF (5 mL), was added 332 mg (2.10 mmol) of commercial 4-trifluoromethyl benzaldehyde. The solution was allowed 24h at room temperature. After removal of the solvent, the residue was treated with diethyl ether and the precipitate filtred washed with ice-cold ethanol and dried under *vacum* to give 0.721 g of a pale yellow solid (98%).

m.p. = 229 °C

Preparation of (2-Methyl-5-nitro-phenyl)-[5-(4-trifluoromethyl-phenyl)-[1,3,4] thiadiazol-2-yl]-amine

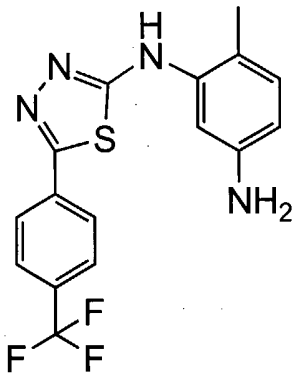


To a stirred solution of *N'*-(4-Trifluoromethyl-benzylidene)-hydrazinecarbothioic acid *N*-(2-methyl-5-nitro-phenyl) amide (163 mg, 0.426 mmol) in EtOH (5 mL), iron (III) chloride was added under nitrogen at room temperature. The mixture was then refluxed for 4h. After cooling, the solution was slightly concentrated. After filtering,

the collected precipitate was dissolved in methanol and alkalized with diluted aqueous ammonia. The organic layer was evaporated and the residue recrystallized from acetonitrile to give 67 mg (89%) of yellow crystals.

m.p. = 194 °C

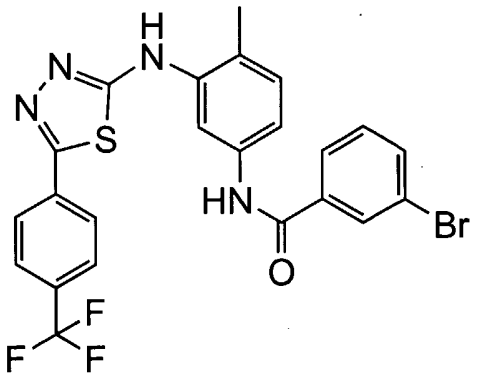
Preparation of 4-Methyl-*N*3-[5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-benzene-1,3-diamine



To a solution of (2-Methyl-5-nitro-phenyl)-[5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (300 mg, 0.79 mmol) in ethanol (15 mL) was added tin(II) chloride dihydrate (1.1 g, 5.12 mmol). The reaction mixture was heated under reflux for 5h. The mixture was then concentrated, saturated aqueous $NaHCO_3$ was added and the resultant suspension was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was silica gel column chromatographed (dichloromethane/ethanol : 97/3). 221 mg (52%) of 4-Methyl-*N*3-[5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-benzene-1,3-diamine was obtained as yellow powder.

m.p. = 187°C

Preparation of 3-Bromo-*N*-{4-methyl-3-[5-(4-trifluoromethyl-phenyl)-[1,3,4] thiadiazol-2-ylamino]-phenyl}-benzamide

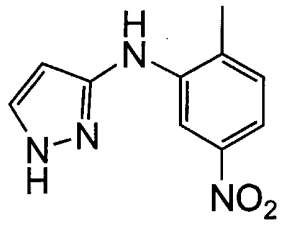


To a solution of 4-Methyl-*N*3-[5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-benzene-1,3-diamine (60 mg, 0.17 mmol) and 3-Bromo-benzoic acid (38 mg, 0.279 mmol) in DMF (4 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (48 mg, 0.25 mmol), 1-hydroxybenzotriazole (30 mg, 0.22 mmol) and triethylamine (0.030 ml, 0.355 mmol). The mixture was stirred at room temperature for 24h. After removal of the solvent, the residue was treated with saturated aqueous $NaHCO_3$ (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. 3-Bromo-*N*-{4-methyl-3-[5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-ylamino]-phenyl}-benzamide was obtained after silica gel column chromatography (dichloromethane/ethanol : 98/2) (20 mg , 22%) as white solid.

m.p. = 231 °C

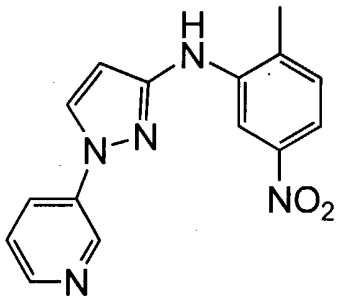
^{1}H NMR (DMSO-d^6) δ = 2.28 (s, 3H) ; 7.25 (d, J = 8.3 Hz, 1H) ; 7.52 (m, 2H) ; 7.78 (d, J = 7.8 Hz, 1H) ; 7.85 (d, J = 8.4 Hz, 2H) ; 7.95 (d, J = 7.8 Hz, 1H) ; 8.05 (d, J = 8.2 Hz, 2H) ; 8.15 (br s, 1H) ; 8.27 (br s, 1H) ; 9.75 (br s, 1H) ; 10.39 (br s, 1H).

Preparation of (2-Methyl-5-nitro-phenyl)-(1*H*-pyrazol-3-yl)-amine



To a solution of Hydrazinecarbothioic acid *N*-(2-methyl-5-nitro-phenyl)amide (820 mg, 3.6 mmol) in ethanol (10 mL) was slowly added concentrated HCl (4.5 mL) at room temperature. After the mixture stirred for 10 min., a solution of Chloroacetaldehyde (0.63 mL) in ethanol (25 mL) was added drop wise resulting in a gradual dissolution of the suspension. After 4h sulfur was removed by filtration and the solid was recrystallized from ethanol to yield 505 mg (62%) as a white powder.

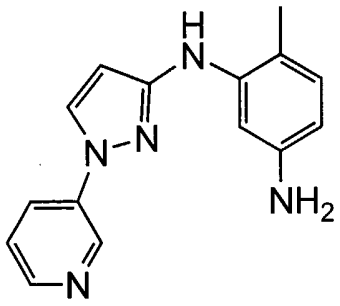
Preparation of (2-Methyl-5-nitro-phenyl)-(1-pyridin-3-yl-1*H*-pyrazol-3-yl)-amine



A solution of 3-pyridyl boronic acid (0.91 mg, 7.4 mmol), aminoarylpyrazole (0.80 g, 3.7 mmol), anhydrous cupric acetate (1 g, 5.5 mmol), pyridine (9.5 mL) in dichloromethane, was stirred at room temperature 48h. The mixture was filtred through celite, washed with methanol and purified by alumina gel column chromatography (dichloromethane/ethanol : 98/1) to give 280 mg (26%) as yellow solid.

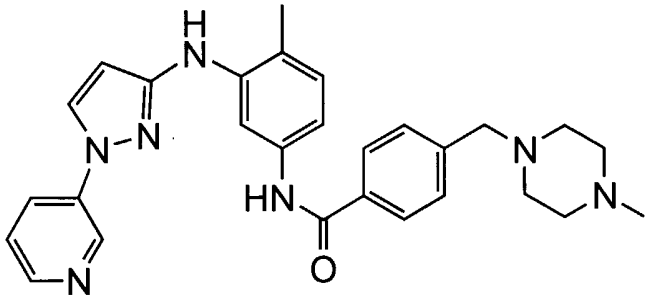
m.p. > 260 °C

Preparation of 4-Methyl-*N*3-(1-pyridin-3-yl-1*H*-pyrazol-3-yl)-benzene-1,3-diamine



To a solution of (2-Methyl-5-nitro-phenyl)-(1-pyridin-3-yl-1*H*-pyrazol-3-yl)-amine (145 mg, 0.59 mmol) in ethyl acetatel (20 mL) was added tin(II) chloride dihydrate (1.33 g, 5.90 mmol). The reaction mixture was heated under reflux for 3h. The mixture was then concentrated, saturated aqueous $NaHCO_3$ was added and the resultant suspension was extracted with ethyl acetate (3×250 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was alumina gel column chromatographed (dichloromethane/ethanol : 99/1). 82 mg (62%) of 4-Methyl-*N*3-(1-pyridin-3-yl-1*H*-pyrazol-3-yl)-benzene-1,3-diamine was obtained as pale yellow powder.

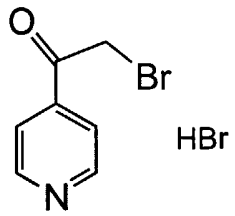
Preparation 4-(4-Methyl-piperazin-1-ylmethyl)-*N*-[4-methyl-3-(1-pyridin-3-yl-1*H*-pyrazol-3-ylamino)-phenyl]-benzamide



A 2M solution of trimethyl aluminium in hexane (0.42 mL, 0.84 mmol) was added dropwise to a cold (0° C) solution of 4-Methyl-*N*3-(1-pyridin-3-yl-1*H*-pyrazol-3-yl)-benzene-1,3-diamine (75 mg, 0.28 mmol) in anhydrous dichloromethane (5 mL) under argon atmosphere. The mixture was warmed to room temperature and stirred at room temperature for 3h. A solution of methyl-4-(1-N-methyl-piperazino)-methyl benzoate (70 mg, 0.28 mmol) in anhydrous dichloromethane (1 mL) and added slowly, and the resulting mixture was heated at reflux for 12h. The mixture was cooled to 0°C and quenched by dropwise addition of a 4N aqueous sodium hydroxide solution (2 mL). The mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine (3×15 mL) and dried over anhydrous $MgSO_4$. 4-(4-Methyl-piperazin-1-ylmethyl)-*N*-[4-methyl-3-(1-pyridin-3-yl-1*H*-pyrazol-3-ylamino)-phenyl]-benzamide is obtained in 22% (28 mg) after purification by alumina column chromatography (dichloromethane/ ethanol, 99 :1).

m.p. = 154-155 °C

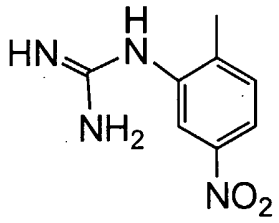
Preparation of 2-Bromo-1-pyridin-4-yl-ethanone hydrobromide



Dibromine (17.2g, 108 mmol) was added drop wise to a cold (0°C) solution of 3-acetyl-pyridine (12 g, 99 mmol) in acetic acid containing 33% of HBr (165 mL) under vigourous stirring. The vigorously stirred mixture was warmed to 40°C for 2h and then to 75°C. After 2h at 75°C, the mixture was cooled and diluted with ether (400 mL) to precipitate the product, which was recovered by filtration and washed with ether and acetone to give white crystals (100%). This material may be recrystallized from methanol and ether.

^{1}H NMR (DMSO-d^6) δ = 5.17 (s, 2H) ; 8.32 (dd, J = 6.1-1.6 Hz, 2H) ; 9.12 (dd, J = 6.1-1.6 Hz, 2H) ; 12.51 (br s, 1H).

Preparation of *N*-(2-Methyl-5-nitro-phenyl)-guanidine

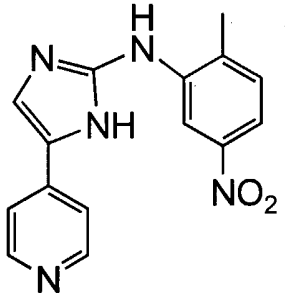


2-methyl 5-nitroaniline (2.00 g, 13 mmol) and cyanamide (1.66 g, 3.0 eq) were dissolved in m-cresol (3 ml) in presence of HCl 12N (1.32 ml). The mixture was stirred for 10 h. at 100°C. After cooling, the mixture was treated with NaOH 2.5 N (15 mL) and extracted with ethyl acetate (2 x 30 ml). The combined organic layers were dried over MgSO4, filtered and evaporated to dryness. The brown oil residue, cooled with an ice bath was dissolved in ethyl ether (4 ml) and NaOH 2.5 N (0.4 ml) was added. The pure expected product was filtered and washed with ethyl ether (2.06 g, 82 %).

m.p. = 149°C (yellow powder)

^{1}H NMR (DMSO, d^6) δ : 2.20 (s, 3H) ; 5.32 (s, 4H) ; 7.34 (d, J = 8.3 Hz, 1H) ; 7.50 (d, J = 1.8 Hz, 1H) ; 7.61 (dd, J = 2.32 Hz, J = 8.18 Hz, 1H)

Preparation of (2-Methyl-5-nitro-phenyl)-(5-pyridin-4-yl-1*H*-imidazol-2-yl)-amine

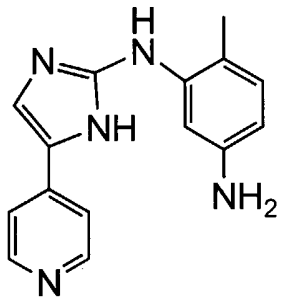


Guanidine (0.100 g, 0.515 mmol) and 4-bromoacetylpyridine, HBr (0.201 g, 1.4 eq) were dissolved in ethanol (4 ml) in presence of $NaHCO_3$ (0.144 g, 2.8 eq). The mixture was stirred for 3 h at 85°C. After cooling, the mixture was treated with a saturated $NaHCO_3$ solution (10 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The pure expected product was obtained after silica gel column chromatography (dichloromethane/ethanol : 9/1) (0.040 g, 26 %).

m.p.>260°C (yellow powder)

^{1}H NMR (DMSO, d^6) δ : 2.29 (s, 3H) ; 5.80 (s, 2H) ; 7.64 (d, J = 6.25 Hz, 3H) ; 7.77 (d, J = 8.52 Hz, 1H) ; 8.20 (d, J = 2.11 Hz, 1H) ; 8.31 (dd, J = 8.53 Hz, J = 2.23 Hz, 1H) ; 8.50 (d, J = 5.83 Hz, 1H).

Preparation of 4-Methyl-*N*3-(5-pyridin-4-yl-1*H*-imidazol-2-yl)-benzene-1,3-diamine

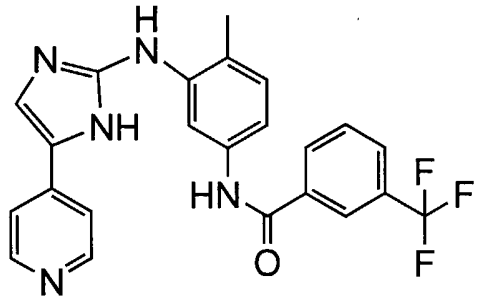


A mixture of nitro compound (0.375 g, 1,27 mmol), iron (0.213 g, 3.0 eq) and HCl 12N (0.025 ml, 0.2 eq) in ethanol 70 % (6.50 ml) was stirred at 95°C for 4 h. After cooling to room temperature, the mixture was diluted with DCM and the reaction mixture was filtered. The filtrate was evaporated to get a residue which was dissolved in ethyl acetate and washed with NaOH 2.5 N, dried over $MgSO_4$, filtered and evaporated to dryness. The solid residue (0.277 g, 82 %) was taken off from ethyl ether.

m.p. = 202°C (beige powder)

^{1}H NMR (DMSO, d^6) δ : 1.97 (s, 3H) ; 5.22 (s, 1H) ; 5.40 (s, 1H) ; 6.51 (d, J = 2.20 Hz, 1H) ; 6.63 (dd, J = 8.12 Hz, J = 2.20 Hz, 1H) ; 7.06 (d, J = 8.29 Hz, 1H) ; 7.50 (s, 1H) ; 7.62 (d, J = 6.05 Hz, 2H) ; 8.46 (d, J = 6.01 Hz, 2H).

Preparation of *N*-[4-Methyl-3-(5-pyridin-4-yl-1*H*-imidazol-2-ylamino)-phenyl]-3-trifluoro methyl-benzamide



To a solution of the amine (0.070 g, 0.264 mmol) and 3 trifluoromethyl benzoic acid (0.060 g, 1.2 eq) in DMF (6 ml) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.071 g, 1.5 eq), 1-hydroxybenzotriazole (0.046 g, 1.3 eq) and triethylamine (0.055 ml, 1.5 eq). The mixture was stirred at room temperature for 48 h. After removal of the solvent, the residue was treated with saturated aqueous. $NaHCO_3$ (20 ml) and extracted with DCM (3 x 30 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$, filtered and evaporated. The pure expected product was obtained after an Alumina gel column chromatography (dichloromethane/ethanol : 98/2) (0.063 g, 55%)

m.p.>260°C (Beige powder)

^{1}H NMR (DMSO-d^6) : δ : 2.15 (s, 3H) ; 5.60 (s, 2NH) ; 7.46 (d, 1H) ; 7.62 (m, 3H) ; 7.84 (m, 3H) ; 8.01 (m, 1H) ; 8.31 (m, 2H) ; 8.49 (m, 2H) ; 10.64 (s, 1H).

In a second embodiment, the invention relates to a pharmaceutical composition comprising a compound as depicted above.

Such medicament can take the form of a pharmaceutical composition adapted for oral administration, which can be formulated using pharmaceutically acceptable carriers well known in the art in suitable dosages. 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. 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.).

The composition of the invention can also take the form of a pharmaceutical or cosmetic composition for topical administration.

Such compositions may be presented in the form of a gel, paste, ointment, cream, lotion, liquid suspension aqueous, aqueous-alcoholic or, oily solutions, or dispersions of the lotion or serum type, or anhydrous or lipophilic gels, or emulsions of liquid or semi-solid consistency of the milk type, obtained by dispersing a fatty phase in an aqueous phase or vice versa, or of suspensions or emulsions of soft, semi-solid consistency of the cream or gel type, or alternatively of microemulsions, of microcapsules, of microparticles or of vesicular dispersions to the ionic and/or nonionic type. These compositions are prepared according to standard methods.

The composition according to the invention comprises any ingredient commonly used in dermatology and cosmetic. It may comprise at least one ingredient selected from hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, emollients, viscosity enhancing polymers, humectants, surfactants, preservatives, antioxidants, solvents, and fillers, antioxidants, solvents, perfumes, fillers, screening agents, bactericides, odor absorbers and coloring matter.

As oils which can be used in the invention, mineral oils (liquid paraffin), vegetable oils (liquid fraction of shea butter, sunflower oil), animal oils, synthetic oils, silicone oils (cyclomethicone) and fluorinated oils may be mentioned. Fatty alcohols, fatty acids (stearic acid) and waxes (paraffin, carnauba, beeswax) may also be used as fatty substances.

As emulsifiers which can be used in the invention, glycerol stearate, polysorbate 60 and the PEG-6/PEG-32/glycol stearate mixture are contemplated.

As hydrophilic gelling agents, carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides such as hydroxypropylcellulose, clays and natural gums may be mentioned, and as lipophilic gelling agents, modified clays such as bentones, metal salts of fatty acids such as aluminum stearates and hydrophobic silica, or alternatively ethylcellulose and polyethylene may be mentioned.

As hydrophilic active agents, proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, starch and plant extracts, in particular those of Aloe vera may be used.

As lipophilic active, agents, retinol (vitamin A) and its derivatives, tocopherol (vitamin E) and its derivatives, essential fatty acids, ceramides and essential oils may be used. These agents add extra moisturizing or skin softening features when utilized.

In addition, a surfactant can be included in the composition so as to provide deeper penetration of the compound capable of depleting mast cells, such as a tyrosine kinase inhibitor, preferably a c-kit and/or a bcr-abl inhibitor.

Among the contemplated ingredients, the invention embraces penetration enhancing agents selected for example from the group consisting of mineral oil, water, ethanol, triacetin, glycerin and propylene glycol; cohesion agents selected for example from

the group consisting of polyisobutylene, polyvinyl acetate and polyvinyl alcohol, and thickening agents.

Chemical methods of enhancing topical absorption of drugs are well known in the art. For example, compounds with penetration enhancing properties include sodium lauryl sulfate (Dugard, P. H. and Sheuplein, R. J., "Effects of Ionic Surfactants on the Permeability of Human Epidermis: An Electrometric Study," J. Ivest. Dermatol., V.60, pp. 263-69, 1973), lauryl amine oxide (Johnson et. al., US 4,411,893), azone (Rajadhyaksha, US 4,405,616 and 3,989,816) and decylmethyl sulfoxide (Sekura, D. L. and Scala, J., "The Percutaneous Absorption of Alkylmethyl Sulfides," Pharmacology of the Skin, Advances In Biolocy of Skin, (Appleton-Century Craft) V. 12, pp. 257-69, 1972). It has been observed that increasing the polarity of the head group in amphoteric molecules increases their penetration-enhancing properties but at the expense of increasing their skin irritating properties (Cooper, E. R. and Berner, B., "Interaction of Surfactants with Epidermal Tissues: Physiochemical Aspects," Surfactant Science Series, V. 16, Reiger, M. M. ed. (Marcel Dekker, Inc.) pp. 195-210, 1987).

A second class of chemical enhancers are generally referred to as co-solvents. These materials are absorbed topically relatively easily, and, by a variety of mechanisms, achieve permeation enhancement for some drugs. Ethanol (Gale et. al., U.S. Pat. No. 4,615,699 and Campbell et. al., U.S. Pat. Nos. 4,460,372 and 4,379,454), dimethyl sulfoxide (US 3,740,420 and 3,743,727, and US 4,575,515), and glycerine derivatives (US 4,322,433) are a few examples of compounds which have shown an ability to enhance the absorption of various compounds.

The pharmaceutical compositions of the invention can also be intended for administration with aerosolized formulation to target areas of a patient's respiratory tract.

Devices and methodologies for delivering aerosolized bursts of a formulation of a drug is disclosed in US 5,906,202. Formulations are preferably solutions, e.g. aqueous solutions, ethanoic solutions, aqueous/ethanoic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. For example aerosolized particles comprise the active ingredient mentioned above and a carrier, (e.g., a pharmaceutically active respiratory drug and carrier) which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a flexible porous membrane. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs.

The invention encompasses the systems described in US 5,556,611:

- liquid gas systems (a liquefied gas is used as propellent gas (e.g. low-boiling FCHC or propane, butane) in a pressure container,
- suspension aerosol (the active substance particles are suspended in solid form in the liquid propellent phase),
- pressurized gas system (a compressed gas such as nitrogen, carbon dioxide, dinitrogen monoxide, air is used.

Thus, according to the invention the pharmaceutical preparation is made in that the active substance is dissolved or dispersed in a suitable nontoxic medium and said solution or dispersion atomized to an aerosol, i.e. distributed extremely finely in a carrier gas. This is technically possible for example in the form of aerosol propellent gas packs, pump aerosols or other devices known per se for liquid misting and solid atomizing which in particular permit an exact individual dosage.

Therefore, the invention is also directed to aerosol devices comprising the compound as defined above and such a formulation, preferably with metered dose valves.

The pharmaceutical compositions of the invention can also be intended for intranasal administration.

In this regard, pharmaceutically acceptable carriers for administering the compound to the nasal mucosal surfaces will be readily appreciated by the ordinary artisan. These

carriers are described in the Remington's Pharmaceutical Sciences" 16th edition, 1980, Ed. By Arthur Osol, the disclosure of which is incorporated herein by reference.

The selection of appropriate carriers depends upon the particular type of administration that is contemplated. For administration via the upper respiratory tract, the composition can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension, for intranasal administration as drops or as a spray. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from pH 6.0 to pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's, Id. at page 1445). Of course, the ordinary artisan can readily determine a suitable saline content and pH for an innocuous aqueous carrier for nasal and/or upper respiratory administration.

Common intranasal carriers include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 3000 cps, or from about 2500 to 6500 cps, or greater, may also be used to provide a more sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington's, cited supra. A preferred alkylcellulose is, e.g., methylcellulose in a concentration ranging from about 5 to about 1000 or more mg per 100 ml of carrier. A more preferred concentration of methyl cellulose is, simply by way of example, from about 25 to about mg per 100 ml of carrier.

Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. For nasal administration of solutions or suspensions

according to the invention, various devices are available in the art for the generation of drops, droplets and sprays.

A premeasured unit dosage dispenser including a dropper or spray device containing a solution or suspension for delivery as drops or as a spray is prepared containing one or more doses of the drug to be administered and is another object of the invention. The invention also includes a kit containing one or more unit dehydrated doses of the compound, together with any required salts and/or buffer agents, preservatives, colorants and the like, ready for preparation of a solution or suspension by the addition of a suitable amount of water.

Another aspect of the invention is directed to the use of said compound to manufacture a medicament. In other words, the invention embraces a method for treating a disease related to unregulated c-kit transduction comprising administering an effective amount of a compound as defined above to a mammal in need of such treatment. It also relates to a method for treating a disease related bcr-abl and/or Flt-3 comprising administering an effective amount of a compound as defined above to a mammal in need of such treatment.

More particularly, the invention is aimed at a method for treating a disease selected from autoimmune diseases, allergic diseases, bone loss, cancers such as leukemia and GIST, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases (IBD), interstitial cystitis, mastocytosis, infections diseases, metabolic disorders, fibrosis, diabetes and CNS disorders comprising administering an effective amount a compound depicted above to a mammal in need of such treatment.

The above described compounds are useful for manufacturing a medicament for the treatment of diseases related to unregulated c-kit transduction, including, but not limited to:

- neoplastic diseases such as mastocytosis, canine mastocytoma, solid tumours, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-

small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, solid tumors and astrocytomas.

- tumor angiogenesis.
- metabolic diseases such as diabetes mellitus and its chronic complications; obesity; type II diabetes; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.
- allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and blood sucking parasitic infestation.
- interstitial cystitis.
- bone loss (osteoporosis).
- inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions as well as inflammatory muscle disorders;
- autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis.
- graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.
- Other autoimmune diseases embraced by the invention active chronic hepatitis and chronic fatigue syndrome.
- subepidermal blistering disorders such as pemphigus.
- Vasculitis.
- HIV infection.

- Plasmodium infection.
- melanocyte dysfunction associated diseases such as hypermelanosis resulting from melanocyte dysfunction and including lentigines, solar and senile lentigo, Dubreuilh melanosis, moles as well as malignant melanomas. In this regard, the invention embraces the use of the compounds defined above to manufacture a medicament or a cosmetic composition for whitening human skin.
- CNS disorders such as psychiatric disorders, migraine, pain, memory loss and nerve cells degeneracy. More particularly, the method according to the invention is useful for the treatment of the following disorders: Depression including dysthymic disorder, cyclothymic disorder, bipolar depression, severe or "melancholic" depression, atypical depression, refractory depression, seasonal depression, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, other syndromes such as mental slowing and loss of concentration, pessimistic worry, agitation, self-deprecation, decreased libido, pain including, acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain, psychogenic pain syndromes, anxiety disorders including anxiety associated with hyperventilation and cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, psychiatric emergencies such as panic attacks, including psychosis, delusional disorders, conversion disorders, phobias, mania, delirium, dissociative episodes including dissociative amnesia, dissociative fugue and dissociative identity disorder, depersonalization, catatonia, seizures, severe psychiatric emergencies including suicidal behaviour, self-neglect, violent or aggressive behaviour, trauma, borderline personality, and acute psychosis, schizophrenia including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia,
- neurodegenerative diseases including Alzheimer's disease , Parkinson's disease, Huntington's disease, the prion diseases, Motor Neurone Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).

- substance use disorders as referred herein include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.
- Cerebral ischemia
- Fibrosis
- Duchenne muscular dystrophy
- fibrodysplasia
- ACNE
- as male contraceptive.

Regarding mastocytosis, the invention contemplates the use of the compounds as defined above for treating the different categories which can be classified as follows:

The category I is composed by two sub-categories (IA and IB). Category IA is made by diseases in which mast cell infiltration is strictly localized to the skin. This category represents the most frequent form of the disease and includes : i) urticaria pigmentosa, the most common form of cutaneous mastocytosis, particularly encountered in children, ii) diffuse cutaneous mastocytosis, iii) solitary mastocytoma and iv) some rare subtypes like bullous, erythrodermic and teleangiectatic mastocytosis. These forms are characterized by their excellent prognosis with spontaneous remissions in children and a very indolent course in adults. Long term survival of this form of disease is generally comparable to that of the normal population and the translation into another form of mastocytosis is rare. Category IB is represented by indolent systemic disease (SM) with or without cutaneous involvement. These forms are much more usual in adults than in children. The course of the disease is often indolent, but sometimes signs of aggressive or malignant mastocytosis can occur, leading to progressive impaired organ function.

The category II includes mastocytosis with an associated hematological disorder, such as a myeloproliferative or myelodysplastic syndrome, or acute leukemia. These malignant mastocytosis does not usually involve the skin. The progression of the disease depends generally on the type of associated hematological disorder that conditiones the prognosis.

The category III is represented by aggressive systemic mastocytosis in which massive infiltration of multiple organs by abnormal mast cells is common. In patients who pursue this kind of aggressive clinical course, peripheral blood features suggestive of a myeloproliferative disorder are more prominent. The progression of the disease can be very rapid, similar to acute leukemia, or some patients can show a longer survival time.

Finally, **the category IV** of mastocytosis includes the mast cell leukemia, characterized by the presence of circulating mast cells and mast cell progenitors representing more than 10% of the white blood cells. This entity represents probably the rarest type of leukemia in humans, and has a very poor prognosis, similar to the rapidly progressing variant of malignant mastocytosis. Mast cell leukemia can occur either *de novo* or as the terminal phase of urticaria pigmentosa or systemic mastocytosis.

The invention also contemplates the method as depicted for the treatment of recurrent bacterial infections, resurging infections after asymptomatic periods such as bacterial cystitis. More particularly, the invention can be practiced for treating FimH expressing bacteria infections such as Gram-negative enterobacteria including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobactor freudii* and *Salmonella typhimurium*.
In this method for treating bacterial infection, separate, sequential or concomitant administration of at least one antibiotic selected bacitracin, the cephalosporins, the penicillins, the aminoglycosides, the tetracyclines, the streptomycins and the

macrolide antibiotics such as erythromycin; the fluoroquinolones, actinomycin, the sulfonamides and trimethoprim, is of interest.

In one preferred embodiment, the invention is directed to a method for treating neoplastic diseases such as mastocytosis, canine mastocytoma, solid tumours, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In one other preferred embodiment, the invention is directed to a method for treating allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and blood sucking parasitic infestation comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative

glomerulonephritis comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow comprising administering a compound as defined herein to a human in need of such treatment.

Example : in vitro TK inhibition assays

- **Procedures**
  - **C-Kit WT and mutated C-Kit (JM) assay**

Proliferation assays

Cells were washed two times in PBS before plating at 5 x 10_4 cells per well of 96-well plates in triplicate and stimulated either with hematopoietic growth factors (HGF) or without. After 2 days of culture, 37 Bq (1.78 Tbq/mmol) of [$_3$H] thymidine (Amersham Life Science, UK) was added for 6 hours. Cells were harvested and filtered through glass fiber filters and [^{3}H] thymidine incorporation was measured in a scintillation counter.

For proliferation assay, all drugs were prepared as 20mM stock solutions in DMSO and conserved at -80°C. Fresh dilutions in PBS were made before each experiment. DMSO dissolved drugs were added at the beginning of the culture. Control cultures were done with corresponding DMSO dilutions. Results are represented in percentage by taking the proliferation without inhibitor as 100%.

Cells

Ba/F3 murine kit and human kit, Ba/F3 mkitΔ27 (juxtamembrane deletion) are derived from the murine IL-3 dependent Ba/F3 proB lymphoid cells. The FMA3 and P815 cell lines are mastocytoma cells expressing endogenous mutated forms of Kit, i.e., frame deletion in the murine juxtamembrane coding region of the receptor-codons 573 to 579. The human leukaemic MC line HMC-1 expresses mutations JM-V560G;

Immunoprecipitation assays and western blotting analysis

For each assay, 5.10_6 Ba/F3 cells and Ba/F3-derived cells with various c-kit mutations were lysed and immunoprecipitated as described (Beslu *et al.*, 1996), excepted that cells were stimulated with 250 ng / ml of rmKL. Cell lysates were immunoprecipitated with a rabbit immunserum anti murine KIT, directed against the KIT cytoplasmic domain (Rottapel *et al.*, 1991). Western blot was hybridized either with the 4G10 anti-phosphotyrosine antibody (UBI) or with the rabbit immunserum anti-murine KIT or with different antibodies (described in antibodies paragraph). The membrane was then incubated either with HRP-conjugated goat anti mouse IgG antibody or with HRP-conjugated goat anti rabbit IgG antibody (Immunotech), Proteins of interest were then visualized by incubation with ECL reagent (Amersham).

- Experimental results

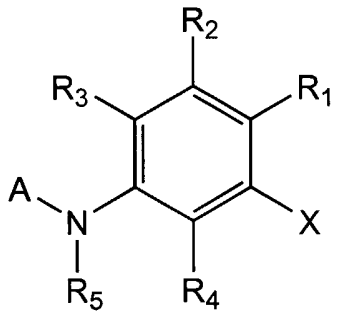
The experimental results for various compounds according to the invention using above-described protocols are set forth at Table 1:

Table 1: in vitro inhibitions of various compounds against c-Kit WT and c-Kit JMΔ27

Target	IC50 (μM)	Compounds
c-Kit WT	IC50 < 10 μM	004, 008, 011, 012, 013, 018
c-Kit JM Δ27	IC50 < 1 μM	011, 012

CLAIMS

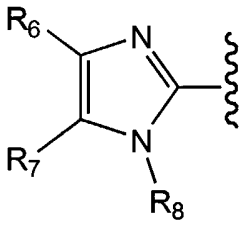
1. A compound of formula I:



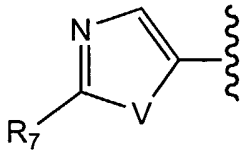
FORMULA I

Wherein A is selected from the group consisting of:

- Imidazole (formula I-1)

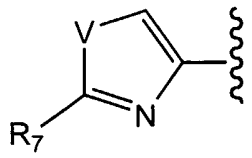


- 5-Aminothiazole/oxazole (formula I-2)



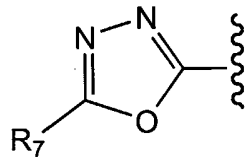
V = S or O

- 4-Aminothiazole/oxazole (formula I-3)

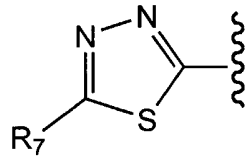


V = S or O

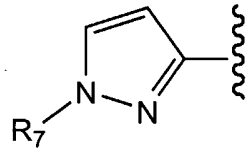
- Oxadiazole (formula I-4)



- Thiadiazole (formula I-5)



- Pyrazole (formula I-6)



Substituents R1 – R8 and X in Formula I 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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of an amino group; as well as trifluoromethyl, C_{1-6}alkyloxy, amino, C_{1-6}alkylamino, di(C_{1-6}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 an amino group.

R5 and R8 are 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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of an amino group, or

(iii) CO-R or COOR or CONHR or SO2R wherein R may be

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

- a heteroaryl group such as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, -heterocycleyl, pyrazolyl, pyrrolyl, furanyl, -heterocycleyl, is-heterocycleyl, triazolyl, tetrazolyl, indolyl, benz-heterocycle, 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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of an amino group; as well as trifluoromethyl, $C_{1\text{-}6}$alkyloxy, carboxyl, cyano, nitro, formyl, hydroxy, $C_{1\text{-}6}$alkylamino, di($C_{1\text{-}6}$alkyl)amino, and amino, the latter nitrogen substituents optionally in the form of an amino group; 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 an amino group.

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 hetereoatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of an amino group); 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 an amino group ; as well as a cycloalkyl or aryl or heteroaryl group optionally substituted by a an amino group, 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 an amino group;
- 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 an amino group;
- 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, -heterocycleyl, pyrazolyl, pyrrolyl, furanyl, -heterocycleyl, is-heterocycleyl , triazolyl, tetrazolyl, indolyl, benz-heterocycle, 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 an amino group,
- 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 an amino group;
- 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 hydrogern, alkyl[1], or

(v) an O-aryl[1], or NH-aryl[1], or O-heteroaryl[1] or NH-heteroaryl[1] group

(vi) trifluoromethyl, O-alkyl[1], carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl[1], N(alkyl[1])(alkyl[1]), and amino, the latter nitrogen substituents optionally in the form of an amino group, or

(vi) NHCO-R or NHCOO-R or NHCONH-R or NHSO2-R or NHSO2NH-R or CO-R or COO-R or CONH-R or SO2-R or SO2NH-R wherein R corresponds to hydrogen, alkyl[1], aryl or heteroaryl.

X is:

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

i) an alkyl[1] group, CF3 or

ii) an aryl[1], heteroaryl[1] or cycloalkyl group optionally substituted by a an amino group, or

iii) a CO-R, COO-R, CON-RR'or SO2-R, where R and R' are a hydrogen, alkyl[1], aryl[1] or heteroaryl[1], optionally substituted by a an amino group;

or:

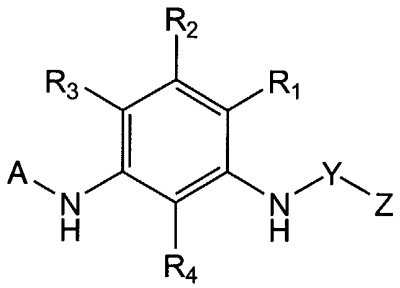
-CO-NR9R10, wherein R9 and / or R10 are hydrogen or:

i) an alkyl[1] group, CF3 or

ii) an aryl[1], heteroaryl[1] or cycloalkyl group optionally substituted by a an amino group.

- alkyl[1]

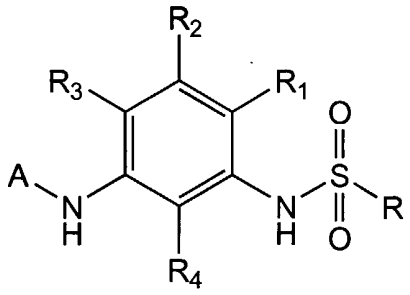
2. A compound according to claim 1 of formula II:



FORMULA II

wherein Y and Z represents an hydrogen, an aryl[1] or a heteroaryl[1] group, optionally substituted by a pendant basic nitrogen functionality and wherein A, R1, R2, R3 and R4 have the meaning as defined in claim 1.

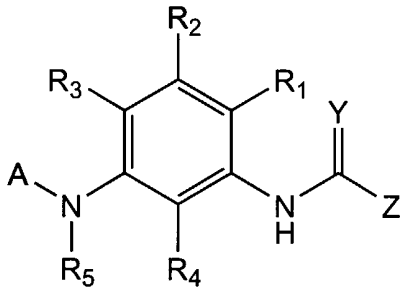
3. A compound according to claim 1 of formula III :



FORMULA III

R represent an hydrogen, an alkyl[1], aryl[1] or a heteroaryl[1] group, optionally substituted by a pendant basic nitrogen functionality and wherein A, R1, R2, R3 and R4 have the meaning as defined in claim 1.

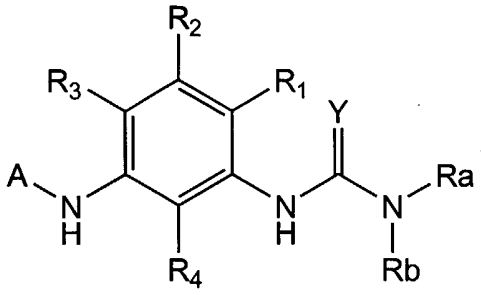
4. A compound according to claim 1 of formula IV :



FORMULA IV

Wherein Y is selected from O, S and Z corresponds to H, NRaRb, alkyl[1], aryl[1], OR wherein Ra, Rb and R are independently chosen from H or alkyl[1] or aryl[1] or heteroaryl[1], optionally substituted by an amino group and wherein A, R1, R2, R3, R4 and R5 have the meaning as defined in claim 1.

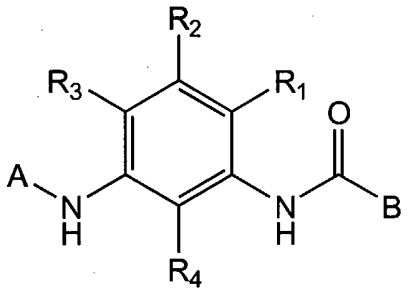
5. A compound according to claim 4 of formula V:



FORMULA V

Wherein Y = O or S and Ra, Rb are independently chosen from H or alkyl[1] or aryl[1] or heteroaryl[1], optionally substituted by an amino group and wherein A, R1, R2, R3 and R4 have the meaning as defined in claim 1.

6. A compound according to claim 4 of formula VI:

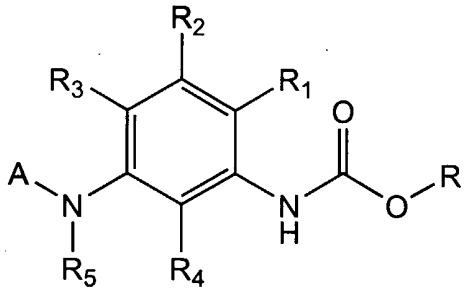


FORMULA VI

Wherein B is aryl[1] or heteroaryl[1] and

wherein A, R1, R2, R3, R4, aryl[1], heteroaryl[1] have the meaning as defined in claim 1.

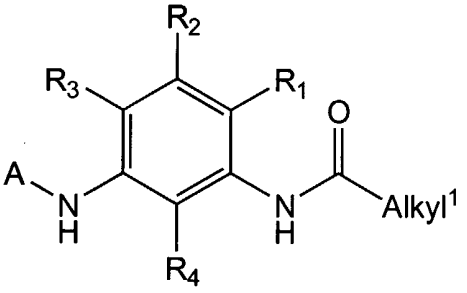
7. A compound according to claim 4 of formula VII:



FORMULA VII

Wherein R is independently alkyl[1], aryl[1] or heteroaryl[1] and wherein A, R1, R2, R3, R4, R5 have the meaning described as defined in claim 1.

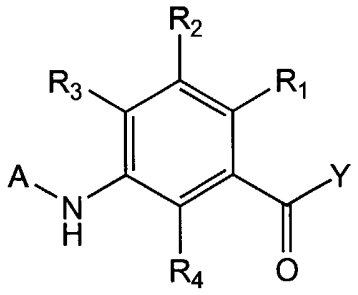
8. A compound according to claim 4 of formula VIII:



FORMULA VIII

Wherein A, R1, R2, R3, R4 and alkyl[1] have the meaning as defined in claim 1.

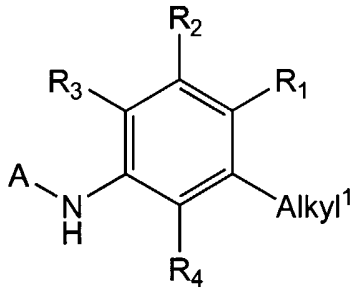
9. A compound according to claim 1 of formula IX:



FORMULA IX

Wherein Y is selected from NRaRb, NHNRaRb, alkyl[1], aryl[1], Ra wherein Ra and Rb are independently chosen from H or alkyl[1] or aryl[1] or heteroaryl[1], optionally substituted by an amino group and wherein A, R1, R2, R3 and R4 have the meaning as defined in claim 1.

10. A compound according to claim 1 of formula X:



FORMULA X

Wherein alkyl[1], A, R1, R2, R3 and R4 have the meaning as defined in claim 1.

11. A pharmaceutical composition comprising a compound according to one of claims 1 to 10.

12. A pharmaceutical composition according to claim 11 further comprising a pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to claim 12 formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, and suspensions.

14. A cosmetic or pharmaceutical composition for topical administration comprising a compound according to one of claims 1 to 10.

15. Use of a compound according to one of claims 1 to 10 to manufacture a medicament.

16. Use of a compound according to one of claims 1 to 10 to manufacture a medicament for treating neoplastic diseases such as mastocytosis, canine mastocytoma, solid tumours, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, myeloma 414, colorectal carcinomas, gastric carcinomas, badder gastrointestinal stromal tumors, testicular cancers, glioblastomas, astrocytomas, bladder cancer and cancer in the airway tracts.

17. Use of a compound according to one of claims 1 to 10 to manufacture a medicament for treating allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and blood sucking parasitic infestation.

18. Use of a compound according to one of claims 1 to 10 to manufacture a medicament for treating inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

19. Use of a compound according to one of claims 1 to 10 to manufacture a medicament for treating autoimmune diseases such as multiple sclerosis, psoriasis,

intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis.

20. Use of a compound according to one of claims 1 to 10 to manufacture a medicament for treating graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.