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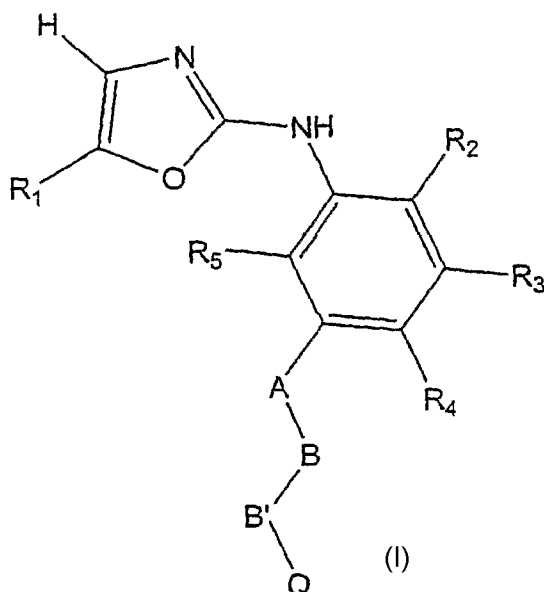
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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

[Continued on next page]

(54) Title: SUBSTITUTED OXAZOLE DERIVATIVES AND THEIR USE AS TYROSINE KINASE INHIBITORS



(57) Abstract: The present invention relates to novel compounds selected from substituted oxazole derivatives of formula (I) 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. More particularly, these compounds are potent and selective c-kit, bcr-abl and Fit-3 inhibitors.



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Substituted oxazole derivatives and their use as tyrosine kinase inhibitors

5

The present invention is concerned with substituted oxazole derivatives 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.

10

More particularly, these compounds are potent and selective c-kit, bcr-abl and Flt-3 inhibitors.

15

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.

20

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.

25

Among tyrosine kinase receptors, c-kit is of special interest. Indeed, c-kit is a key receptor activating mast cells, which have proved 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, US 60/359,652, US 60/359651 and US 60/449861.

30

It was found that mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (rheumatoid arthritis, inflammatory bowel diseases (IBD)) allergic diseases, bone loss, cancers such as solid tumors, leukaemia and GIST, tumor angiogenesis, inflammatory
5 diseases, interstitial cystitis, mastocytosis, graft-versus-host diseases, infection diseases, metabolic disorders, fibrosis, diabetes and CNS diseases. In these diseases, it has been shown that mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators such as histamine, neutral proteases, lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various
10 cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF- α , GM-CSF, MIP-1a, MIP-1b, MIP-2 and IFN- γ).

The c-kit receptor also can be constitutively activated by mutations leading to abnormal cell proliferation and development of diseases such as mastocytosis (D816V
15 mutation) and various cancers such as GIST (c-kit Δ 27, a juxtamembrane deletion).

Sixty to 70% of patients presenting with AML have blasts which express c-kit, the receptor for stem cell factor (SCF) (Broudy, 1997). SCF promotes growth of hematopoietic progenitors, and act as a survival factor for AML blasts. In some cases
20 (1 to 2%) of AML, a mutation in a conserved residue of the kinase domain (Kit816) resulting in constitutive activation of c-kit has been described (Beghini et al., 2000; Longley et al., 2001). This gain of function mutation (Asp to Val/Tyr substitution) has been identified in mast cell leukemic cell lines and in samples derived from patients with mastocytosis (Longley et al., 1996). Preliminary results show that this mutation
25 is expressed in most cases of systemic mastocytosis ([~ 60%], P Dubreuil, AFIRMM, study in progress on about 300 patients).

For this reason, it has been proposed to target c-kit to deplete the mast cells responsible for these disorders.

The main objective underlying the present invention is therefore to find potent and selective compounds capable of inhibiting wild type and/or mutated c-kit.

Many different compounds have been described as tyrosine kinase inhibitors, for example, bis monocyclic, bicyclic or heterocyclic aryl compounds (WO 92/20642),
5 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
10 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
15 722, 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).

However, none of these compounds have been described as potent and selective inhibitors of c-kit or of the c-kit pathway.

20

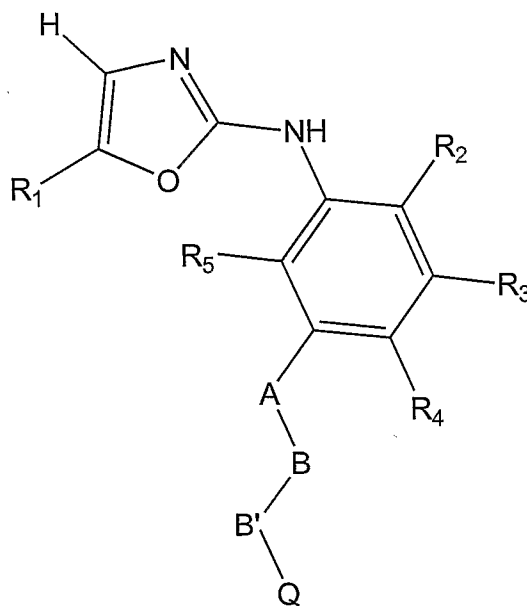
In connection with the present invention, we have discovered that compounds displaying specific substitutions in oxazole derivatives are potent and selective inhibitors of c-kit, bcr-abl, Flt-3 or c-kit pathway. These compounds are good candidates for treating diseases such as autoimmune diseases, inflammatory diseases,
25 cancers and mastocytosis.

Description

Therefore, the present invention relates to compounds belonging to the substituted
30 oxazole derivatives. These compounds are capable of selectively inhibiting signal

transduction involving the tyrosine phosphokinase c-kit, bcr-abl, Flt-3 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 substituents A, B, B', Q and R1 – R5 in Formula I are defined as follows:

A and B' is one of the following:

- i) $(R_6)N(CH_2)_n$ where n is 0 or 1
- ii) $O(CH_2)_n$ where n is 0 or 1
- 15 iii) $S(CH_2)_n$ where n is 0 or 1
- iv) $(CH_2)_n$ where n is 0, 1 or 2
- v) $C(O)(CH_2)_n$ where n is 0 or 1

or when A and B' each are a nitrogen, they may be taken together to form a bivalent radical of formula :

20 $-(CH_2)_s-X1-(CH_2)_t-$ (a)

where s and t each independently is 1 or 2 and X1 being O, S, NR10, N[C(=O)R10] or (CH2)_n where n is 0 or 1, and wherein each hydrogen in said formula (a) may be substituted with halo or C₁₋₄alkyl.

5 B is one of the following:

i) (R6)N

ii) Oxygen

iii) S(O)_n where n is 0, 1 or 2

iv) CH(R6)(R7)

10 v) C=δ, where δ is oxygen, sulfur, NH or N-CN

vi) C(R6)=C(R7)

vii) N=C(R6)

15 R6 and R7 each independently are hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄alkylamino.

R1 is selected from:

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

20 ii) an alkyl¹ group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl, cyano, nitro, formyl; as well as CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing 1 to 10 carbon
25 atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality ; as well as a cycloalkyl or aryl¹ or heteroaryl¹ group optionally substituted by a pendant basic nitrogen functionality, or
30 iii) an aryl¹ group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as

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

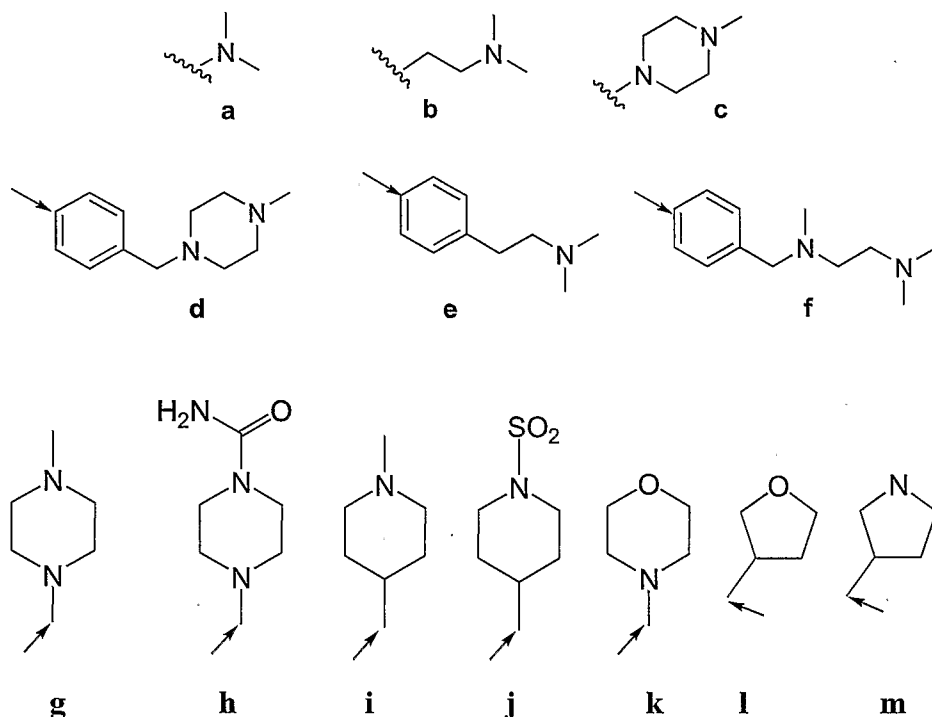
vi) NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl¹ or heteroaryl¹.

- 5 R₂, R₃, R₄ and R₅ each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino,
- 10 C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, CONH-R, SO₂-R, and SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl.

and wherein Q is selected from:

- 15 i) Alkyl¹
 ii) Aryl¹
 iii) Heteroaryl¹
 as defined above.

- 20 In one particular embodiment, group Q is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures **a** to **m** shown below, wherein the wavy line and the arrow line correspond to the point of attachment to core structure of formula **I**.



5

Also, for **g** to **m**, the arrow may include a point of attachment to the core structure via a phenyl group.

Furthermore, among the preferred compounds of formula I, II, III and IV, the invention concerns the compounds in which R₁ is pyridyl or benzonitrile which may additionally bear any combination, at any one ring position, of one or more substituents such as

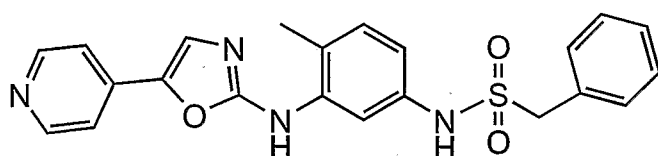
- hydrogen;
- halogen (selected from F, Cl, Br or I);
- an alkyl¹ group;
- an aryl¹ group;
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹ or aryl¹ group.

20

Unless stated otherwise, for the purpose of the present invention, the term “alkyl group” is intended to mean any linear or branched, substituted or unsubstituted, C1-C10 alkyl group, such as C1-C4 or C1-C6, in particular a methyl, ethyl group, propyl group, preferably methyl. The term “alkenyl” as used in the present invention refers to C1-C6, in particular C1-C4, straight or branched chain substituted or unsubstituted alkenyl radicals containing from 1 to 30 carbon atoms including, but not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like. The term “alkoxy group” is intended to mean any alkoxy group having 1 to 6 linear or branched, substituted or unsubstituted, carbon atoms, in particular the group OCH₃. The term “aryl group” is intended to mean one or more aromatic rings having 5 to 6 carbon atoms, which may be joined or fused, and substituted or unsubstituted. In particular, the aryl groups may be phenyl or pyridyl and the substituents may be halogen atoms, cyano, amino, alkoxy groups as defined above, alkyl groups as defined above or a nitro group.

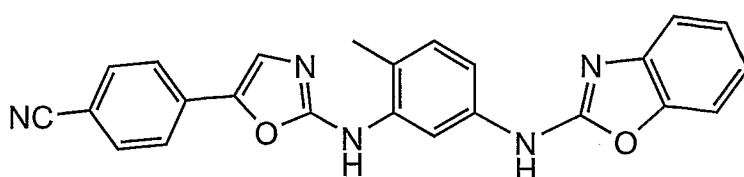
An example of preferred compounds of the above formula is depicted below:

001 : *N*-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-*C*-phenyl-methane sulfonamide



m.p. = 258°C

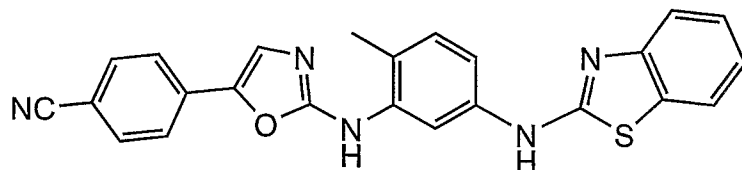
002 : 4-{2-[5-(Benzooxazol-2-ylamino)-2-methyl-phenylamino]-oxazol-5-yl}-benzonitrile



m.p. = 236°C

003 : 4-{2-[5-(Benzothiazol-2-ylamino)-2-methyl-phenylamino]-oxazol-5-yl}-benzonitrile

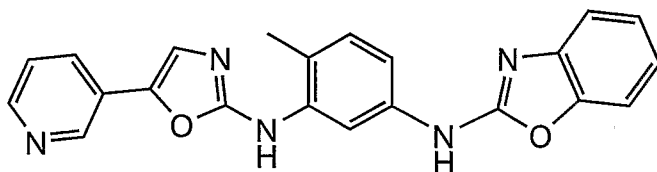
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m.p. = 216-220°C

004 : N1-Benzooxazol-2-yl-4-methyl-N3-(5-pyridin-3-yl-oxazol-2-yl)-benzene-1,3-diamine

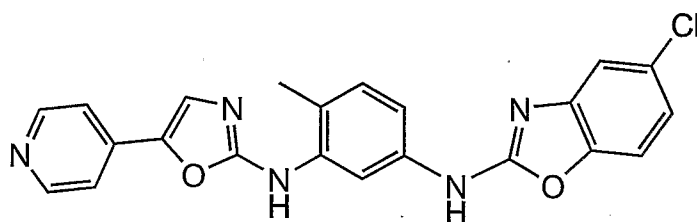
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m.p. = 238°C

005 : N1-(5-Chloro-benzooxazol-2-yl)-4-methyl-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine

15

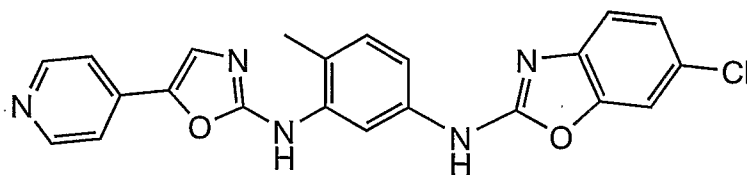


m.p. = 229°C

006 : N1-(6-Chloro-benzooxazol-2-yl)-4-methyl-N3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine

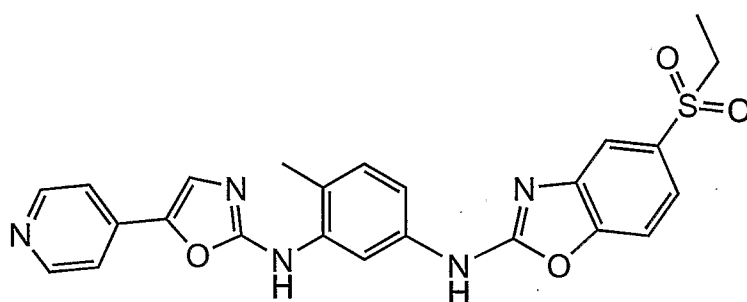
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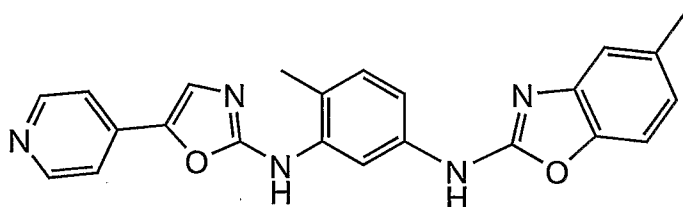
m.p. >260°C

007 : *N*1-(5-Ethanesulfonyl-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine



m.p. =252°C

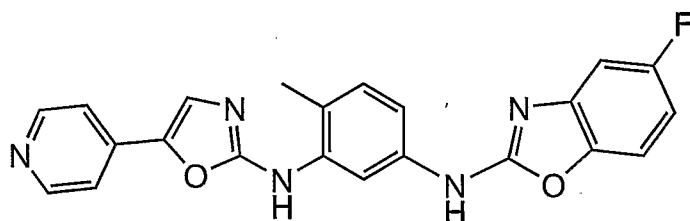
008 : 4-Methyl-*N*1-(5-methyl-benzooxazol-2-yl)-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine



¹H NMR (DMSO-*d*⁶, 300MHz) δ = 2.25 (s, 3H) ; 2.50 (s, 3H) ; 6.91 (d, *J* = 8.1, 1H) ; 7.14 (s, 1H) ; 7.20 (d, *J* = 8.4, 1H) ; 7.33 (d, *J* = 8.1, 1H) ; 7.47-7.53 (m, 3H) ; 7.79 (s, 1H) ; 8.13 (d, *J* = 2.1, 1H) ; 8.53 (s, 1H) ; 8.55 (s, 1H) ; 9.60 (s, 1H) ; 10.53 (s, 1H).

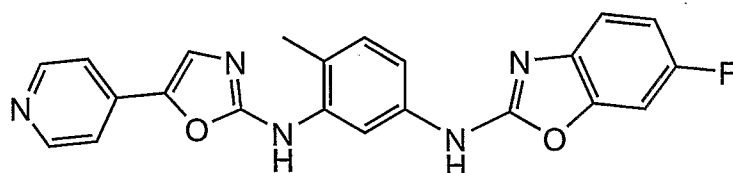
009 : *N*1-(5-Fluoro-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine

12



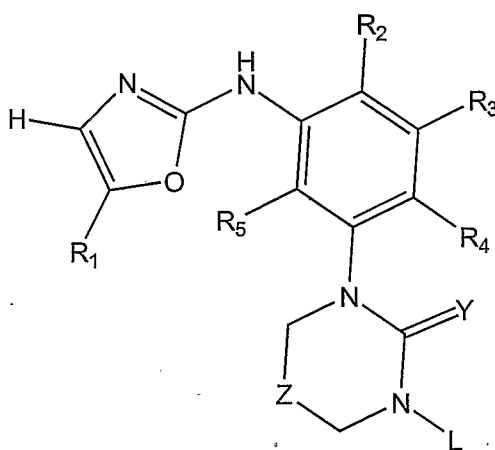
m.p. =170°C

010 : N1-(6-Fluoro-benzooxazol-2-yl)-4-methyl-N3-(5-pyridin-4-yl-oxazol-2-yl)-
5 benzene-1,3-diamine



m.p. =260°C

10 Among the particular compounds of formula I, the invention is directed to compounds
of the following formula II:



15

FORMULA II

Wherein Y is oxygen, sulfur, NH or N-CN, Z is oxygen, sulfur, N(R6) or (CH₂)_n
where n is 0, 1 or 2.

20 L is selected from Alkyl¹, Aryl¹ or Heteroaryl¹ as defined above.

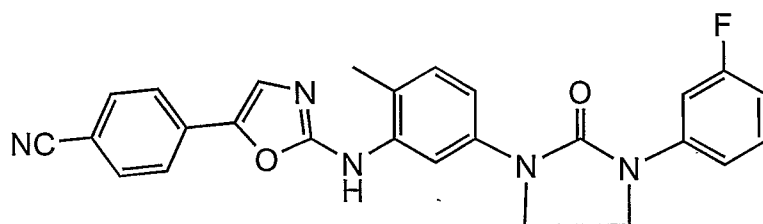
R1, R2, R3, R4, R5 and R6 have the meaning described above.

An example of preferred compounds of the above formula is depicted below:

5

011 : 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile

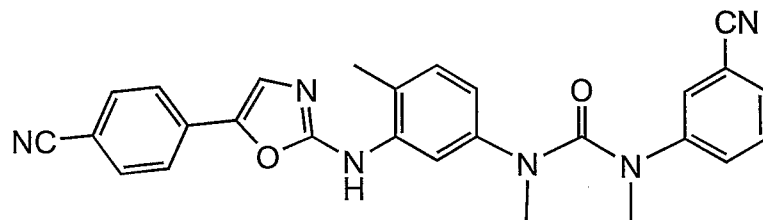
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m.p. =221°C

15

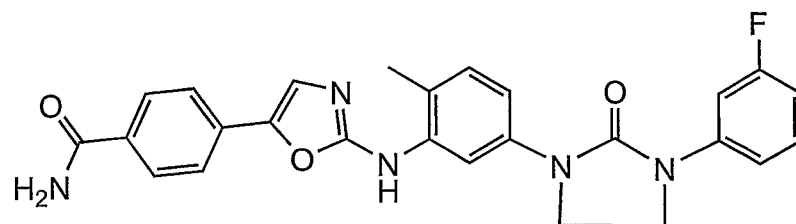
012 : 4-(2-{5-[3-(3-cyano-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile



m.p. >260°C

20

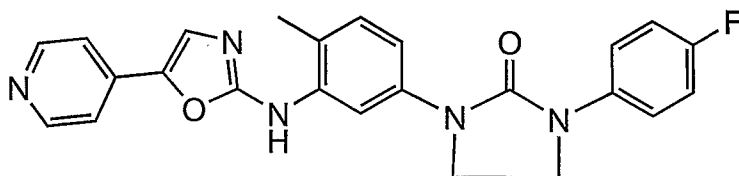
013 : 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzamide



m.p. >260°C

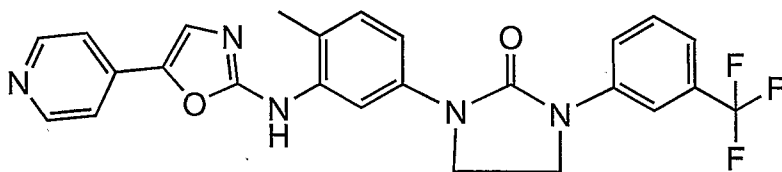
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014 : 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-imidazolidin-2-one



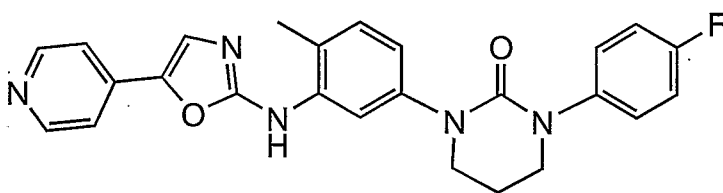
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015 : 1-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-3-(3-trifluoromethyl-phenyl)-imidazolidin-2-one



10 m.p. =198-200°C

016 : 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-tetrahydro-pyrimidin-2-one

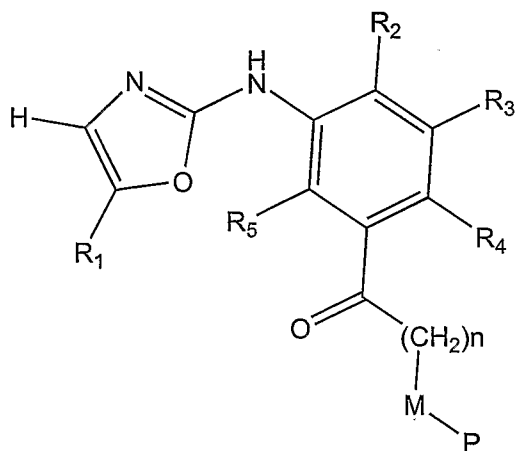


15

Among the particular compounds of formula **I**, the invention is directed to compounds of the following formula **III**:

20

15

**FORMULA III**

5

With n being an integer of 0, 1 or 2.

M is oxygen, sulfur or $(CH_2)_n$ where n is 0, 1 or 2.

P is selected from $N(R_8)(R_9)$, $Alkyl^1$, $Aryl^1$ or $Heteroaryl^1$.

R_8 and R_9 each independently is hydrogen, $Alkyl^1$, $Aryl^1$ or $Heteroaryl^1$.

10 R_8 and R_9 may be taken together to form a bivalent radical of formula :

$-(CH_2)_v-X_2-(CH_2)_w-$ (b)

where v and w each independently is 1 or 2 and X_2 being CH_2 , O, S, NR_{10} or $N[C(=O)R_{10}]$ and wherein each hydrogen in said formula (b) may be substituted with halo or $C_{1-4}alkyl$.

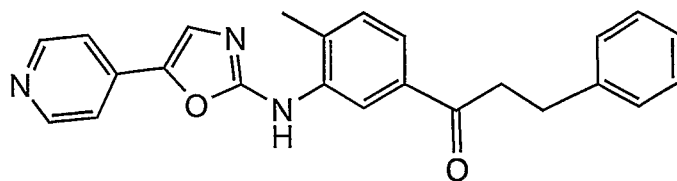
15 R_{10} is hydrogen, $C_{1-4}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-7}cycloalkyl$, $C_{1-4}haloalkyl$, $C_{1-6}alkoxy$, $C_{1-4}hydroxyalkyl$.

R_1 , R_2 , R_3 , R_4 and R_5 have the meaning described above.

20 Examples :

017: 1-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-3-phenyl-propan-1-one

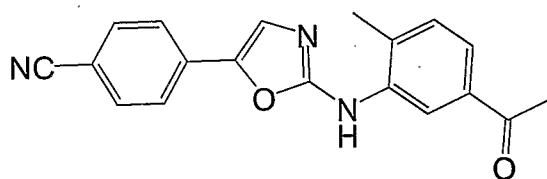
16



m.p. =138°C

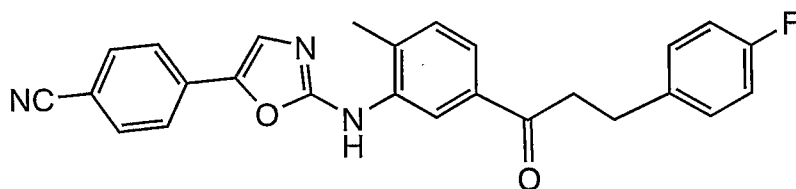
018: 4-[2-(5-Acetyl-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile

5



m.p. =240°C

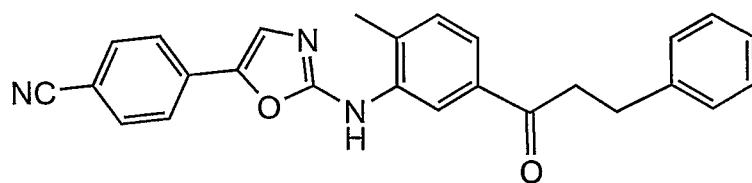
10 019: 4-(2-{5-[3-(4-Fluoro-phenyl)-propionyl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile



m.p. =175°C

15

020: 4-{2-[2-Methyl-5-(3-phenyl-propionyl)-phenylamino]-oxazol-5-yl}-benzonitrile

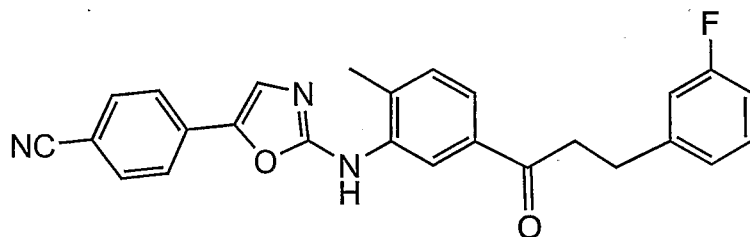


m.p. =138°C

20

021: 4-(2-{5-[3-(3-Fluoro-phenyl)-propionyl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile

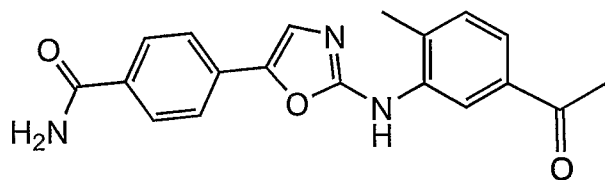
17



m.p. =157°C

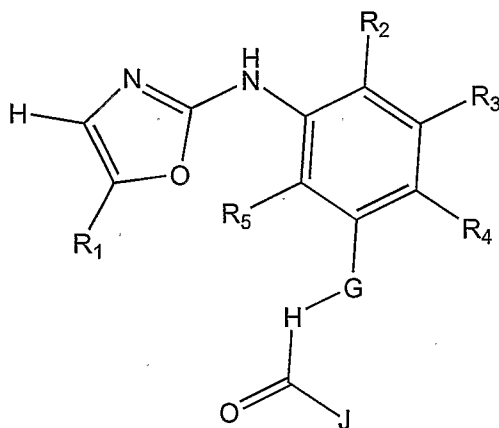
022: 4-[2-(5-Acetyl-2-methyl-phenylamino)-oxazol-5-yl]-benzamide

5



m.p. > 260°C

Among the particular compounds of formula I, the invention is directed to compounds
 10 of the following formula IV:



15

FORMULA IV

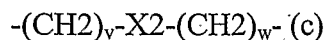
G is oxygen, sulfur, N(R11) or (CH₂)_n where n is 1 or 2.

H is oxygen, N(R11) or (CH₂)_n where n is 1 or 2.

J is selected from N(R12)(R13), Alkyl¹, Aryl¹ or Heteroaryl¹.

20 R12 and R13 each independently is hydrogen, Alkyl¹, Aryl¹ or Heteroaryl¹.

R12 and R13 may be taken together to form a bivalent radical of formula :



where v and w each independently is 1 or 2 and X₂ being CH₂, O, S, NR₁₄ or N[C(=O)R₁₄] and wherein each hydrogen in said formula (c) may be substituted with
5 halo or C₁₋₄alkyl.

R₁₁ and R₁₄ each independently is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₄haloalkyl, C₁₋₆alkoxy, C₁₋₄hydroxyalkyl.

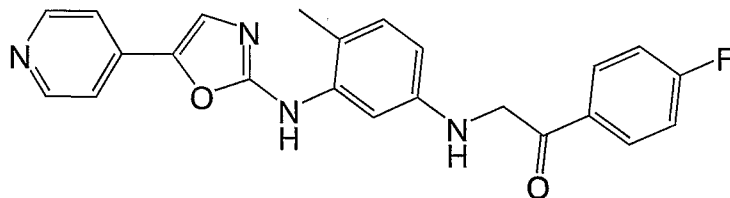
R₁, R₂, R₃, R₄ and R₅ have the meaning described above.

10

Examples:

023: 1-(4-Fluoro-phenyl)-2-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenylamino]-ethanone

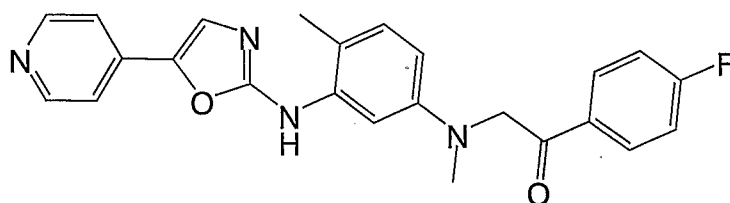
15



m.p. = 202°C

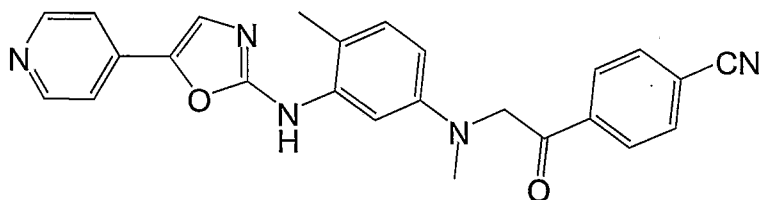
024: 1-(4-Fluoro-phenyl)-2-{methyl-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amino}-ethanone

20



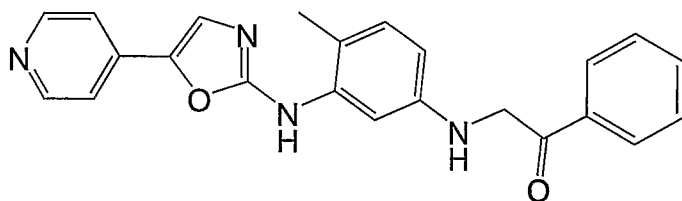
m.p. = 230°C

025: 4-({Methyl-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amino}-acetyl)-benzonitrile



5 m.p. =218°C

026: 2-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenylamino]-1-phenyl-ethanone

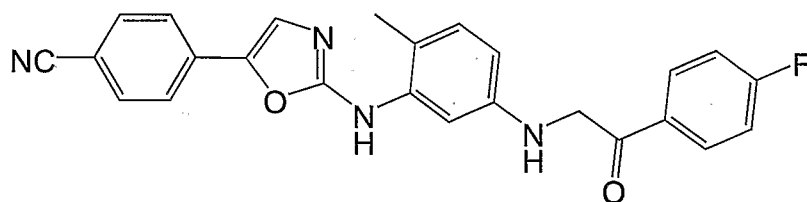


10

m.p. =152°C

027: 4-(2-{5-[2-(4-Fluoro-phenyl)-2-oxo-ethylamino]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile

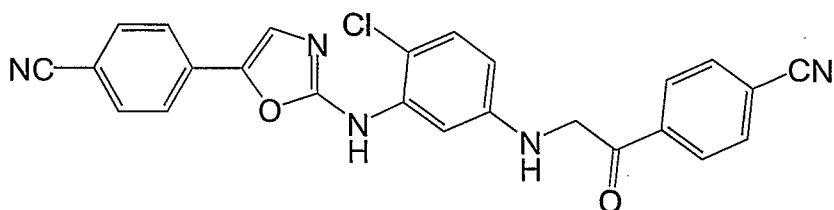
15



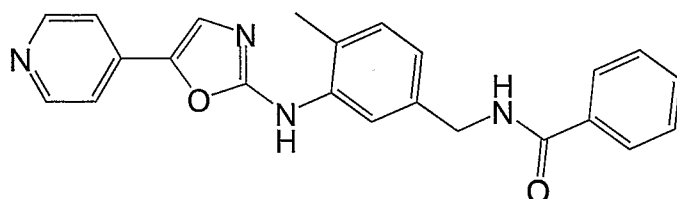
m.p. =199°C

20

028: 4-(2-{5-[2-(4-Cyano-phenyl)-2-oxo-ethylamino]-2-chloro-phenylamino}-oxazol-5-yl)-benzonitrile



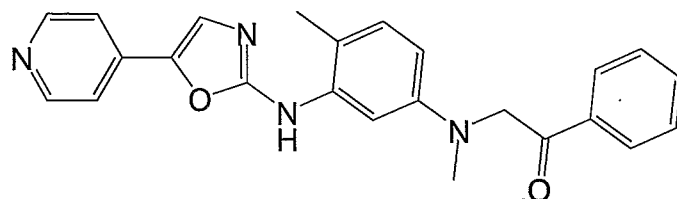
029: N-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-benzyl]-benzamide



5

^1H NMR (DMSO- d^6 , 300MHz) δ = 2.25 (s, 3H) ; 4.45 (d, J = 5.7, 2H) ; 6.99 (d, J = 7.2, 1H) ; 7.17 (d, J = 7.2, 1H) ; 7.45-7.52 (m, 5H) ; 7.72 (s, 2H) ; 7.88 (d, J = 7.2, 2H) ; 8.49 (d, J = 5.1, 2H) ; 9.05 (t, J = 5.7, 1H) ; 9.54 (s, 1H).

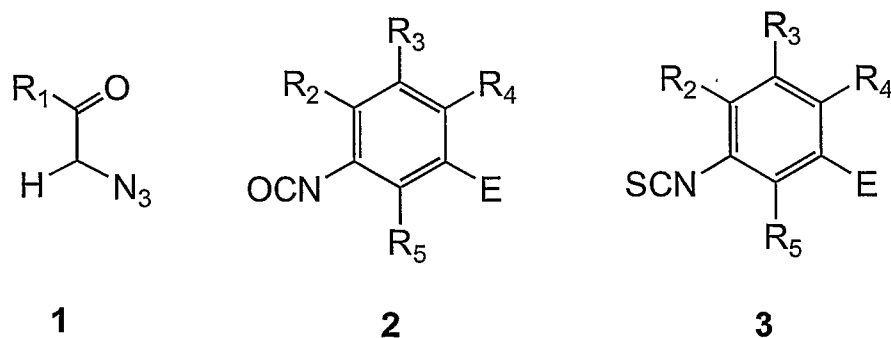
10 030: 2-{Methyl-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amino}-1-phenyl-ethanone



15 ^1H NMR (DMSO- d^6 , 300MHz) δ = 2.14 (s, 3H) ; 3.00 (s, 3H) ; 4.96 (s, 2H) ; 6.37 (d, J = 9.2, 1H) ; 6.95 (d, J = 8.4, 1H) ; 7.13 (s, 1H) ; 7.42 (d, J = 5.4, 2H) ; 7.52-7.65 (m, 4H) ; 7.99 (d, J = 7.2, 2H) ; 8.51 (d, J = 5.7, 2H) ; 9.37 (s, 1H).

20 The compounds of the present invention may be prepared using the general protocole as follows:

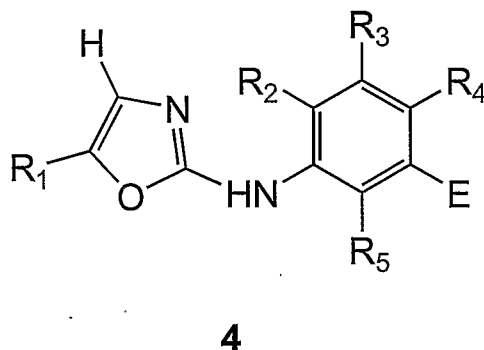
Compounds of formula 4 can be prepared by the condensation of an azide of general formula 1 with an isocyanate of the type 2 or an isothiocyanate of the type 3.



- 5 Group E in formula 2 and 3 corresponds to nitro, cyano, CH₂OH, CO₂CH₃, CONH₂, COCH₃ or to A-B-B'-Q group. A-B-B'-Q group is as described in formula I.

The reaction of 1 either with 2 or 3 in a solvent such as methylene chloride or dioxane in the presence of triphenylphosphine, leads to an oxazole-type product of formula 4.

10



R₁, R₂, R₃, R₄ and R₅ have the meaning described above.

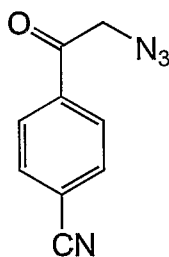
- 15 The following example is intended to illustrate the present invention.

Example of Compound Synthesis

General: All chemicals used were commercial reagent grade products. Solvents were
 20 of anhydrous commercial grade and were used without further purification. Dioxane is

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 ^1H 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.

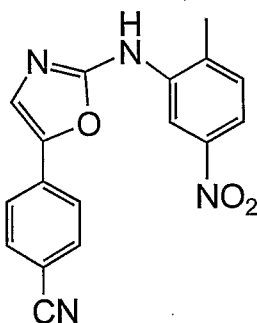
Preparation of 4-Azidoacetyl-benzonitrile



10

To a solution of the commercially available 4-bromoacetyl-benzonitrile (5 g, 22.32 mmol) in 150 mL of methanol was added sodium azide (1.74 g, 26.78 mmol) and the contents stirred at room temperature for 2h. After removal of the solvent, the residue was treated with water (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic layers were dried over MgSO₄ and concentrated to give a yellow solid (3.90 g, 94%). This compound was used for the next step without any further purification.

Preparation of 4-[2-(2-Methyl-5-nitro-phenylamino)-oxazol-5-yl]-benzonitrile

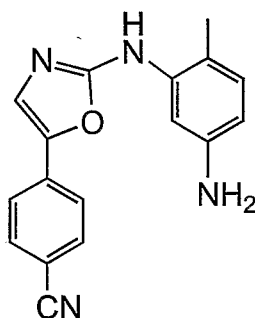


20

To a solution of 4-Azidoacetyl-benzonitrile (1.5 g, 8.06 mmol) in dioxane 25 mL was added 2-methyl-5-nitrophenyl isocyanate (1.43 mg, 8.06 mmol) (commercially available), and triphenylphosphine (2.11 g, 8.06 mmol). The reaction mixture was placed in an oil bath preheated to 100°C and stirred for 30 min. After evaporation of the solvent under reduced pressure, the solid residue was recrystallized from ethanol to give the title compound as yellow micro crystals (1.16 g, 45%).

m.p. > 260°C

10 Preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile

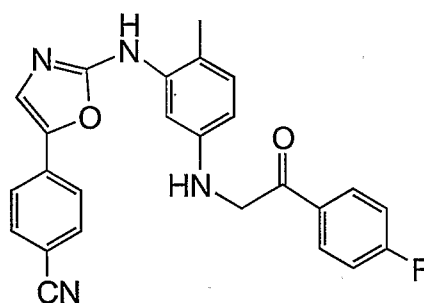


To a solution of 4-[2-(2-Methyl-5-nitro-phenylamino)-oxazol-5-yl]-benzonitrile (500 mg, 1.56 mmol) in ethanol (15 mL) was added tin(II) chloride dihydrate (677 mg, 3 mmol). The reaction mixture was heated under reflux for 4h. The mixture was then concentrated, saturated aqueous NaHCO₃ was added and the resultant suspension was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous MgSO₄ and concentrated. The residue was alumina column chromatographed (dichloromethane/ethanol : 99/1). 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile was obtained as pale yellow powder (172 mg, 38%).

m.p. = 236°C

^1H NMR ($\text{DMSO}-d_6$) δ = 2.14 (s, 3H) ; 4.91 (br s, 2H) ; 6.25 (dd, J = 7.8-1.9, 1H) ; 6.82 (d, J = 8.0, 1H) ; 7.01 (d, J = 2.4, 1H) ; 7.68 (m, 3H) ; 7.84 (d, J = 8.5, 2H) ; 9.22 (s, 1H).

- 5 Preparation of 4-(2-{5-[2-(4-Fluoro-phenyl)-2-oxo-ethylamino]-2-methyl-phenyl-amino}-oxazol-5-yl)-benzonitrile



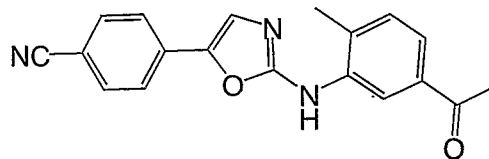
- 10 To a solution of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile (60 mg, 0.207 mmol) in dimethylacetamide (3 mL) was added 4-fluorophenacyl bromide (45 mg, 0.207 mmol), NaHCO_3 (18 mg, 0.207 mmol). The mixture was stirred at room temperature for 2h. After removal of the solvent, the residue was treated with saturated aqueous NaHCO_3 (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 and concentrated.
- 15 4-(2-{5-[2-(4-Fluoro-phenyl)-2-oxo-ethylamino]-2-methyl-phenyl-amino}-oxazol-5-yl)-benzonitrile was obtained after silica gel column chromatography (dichloromethane/ethanol : 98/2) (38 mg, 43%) as beige solid.

m.p. = 199 °C

- 20 ^1H NMR ($\text{DMSO}-d_6$) δ = 2.12 (s, 3H) ; 4.62 (d, J = 4.8, 2H) ; 5.81 (t, J = 4.8, 1H) ; 6.37 (d, J = 6.0, 1H) ; 6.91 (d, J = 8.1, 1H) ; 7.08 (s, 1H) ; 7.37 (m, 2H) ; 7.67 (m, 3H) ; 7.83 (d, J = 8.4, 2H) ; 8.14 (m, 2H) ; 9.30 (s, 1H).

Preparation of 4-[2-(5-Acetyl-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile

25

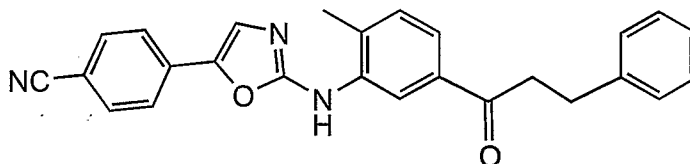


In a similar manner as described for the preparation of 4-[2-(2-Methyl-5-nitro-phenylamino)-oxazol-5-yl]-benzonitrile, from 4-Azidoacetyl-benzonitrile (2.70 g, 14.5 mmol) and 1-(3-Isothiocyanato-4-methyl-phenyl)-ethanone (2.22 g, 11.6 mmol)
 5 was obtained the title compound (1.43, 31%), as a yellow solid.

^1H NMR (DMSO- d^6) δ = 2.41 (s, 3H) ; 2.59 (s, 3H) ; 7.41 (d, J = 7.8, 1H) ; 7.67 (dd, J = 7.8-1.6, 1H) ; 7.75 (s, 1H) ; 7.79 (d, J = 8.4, 2H) ; 7.72 (d, J = 8.4, 2H) ; 8.51 (d, J = 1.6, 1H) ; 9.73 (s, 1H).

10

Preparation of 4-{2-[2-Methyl-5-(3-phenyl-propionyl)-phenylamino]-oxazol-5-yl}-benzonitrile



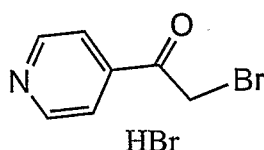
15

To a stirred solution of 4-[2-(5-Acetyl-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile (100 mg, 0.315 mmol) and benzaldehyd (0.035 mL, 0.35 mmol) in ethanol, was added dropwise at 0°C, 1 mL of aqueous NaOH 30%. After the mixture was stirred at room temperature for 16h and poured into ice water (ca. 10 mL). The
 20 precipitate was filtered, washed diethyl ether and dried under vacuum.

The yellow solid obtained was dissolved in ethanol (2 mL) and THF (2 mL), traited with palladium on carbon (10%, 20 mg) and hydrogenated. The catalyst was removed by filtration throught a pad of celite. The filtrate was evaporated under reduce pressure to give the title compound (77 mg, 60%) as yellow powder.

^1H NMR ($\text{DMSO}-d^6$) δ = 2.41 (s, 3H) ; 2.98 (t, J = 7.7, 2H) ; 3.36 (t, J = 7.7, 2H) ; 7.23 (m, 1H) ; 7.32 (m, 4H) ; 7.40 (d, J = 7.8, 1H) ; 7.69 (dd, J = 7.8-1.6, 1H); 7.72 (s, 1H) ; 7.89 (d, J = 8.4, 2H) ; 7.94 (d, J = 8.4, 2H) ; 8.52 (d, J = 1.6, 1H) ; 9.73 (s, 1H).

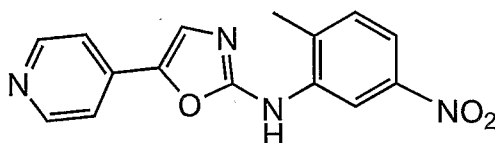
5 Preparation of 4-Bromoacetylpyridine, HBr salt



Bromine (24 g, 150 mmol) in 4 mL of 45% HBr was added drop wise under vigorous stirring to a solution at 70°C of 4-acetyl-pyridine (18 g, 148 mmol) in acetic acid containing 45% of HBr (165 mL). The vigorously stirred mixture was kept at 70°C for 3h. The mixture was cooled and the precipitate collected by filtration and washed with petroleum ether(40-65°C)/methanol (1/1, 100 mL) to give 35.8 g of a white crystals of (85%).

15

Preparation of 2-Methyl-5-nitro-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine



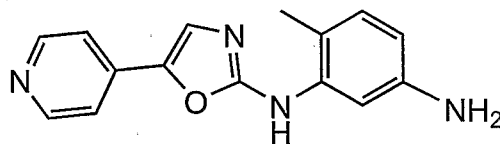
20 To a solution of 4-bromoacetylpyridine hydrobromide (5 g, 17.8 mmol) in 80 mL of water was added sodium azide (1.16 g, 17.8 mmol) and the contents stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C, treated slowly with saturated aqueous NaHCO_3 until pH=6-7, extracted with dichloromethane (3x30mL) and the combined organic phases were dried over MgSO_4 , concentrated at room temperature under reduced pressure to a final volume of 25 mL, and diluted with dioxane (30 mL). The resulting solution was concentrated to remove the remaining

25

(lower boiling) dichloromethane. To the final volume (25 mL) was added at 0°C, 2-methyl-5-nitrophenyl isocyanate (1.58 g, 8.9 mmol) (commercially available) and portion wise triphenylphosphine (2.62 g, 8.9 mmol). The reaction mixture was then stirred for 1 h at room temperature and heated for an additional 2 h at 100°C. After
5 evaporation of the solvent under reduced pressure the residue was crystallized in dichloromethane/ethanol (10mL/5mL), to give the title compound as yellow crystals (0.9 g, 34%).

m p > 220 °C

10 Preparation of (2-Methyl-5-amino-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine

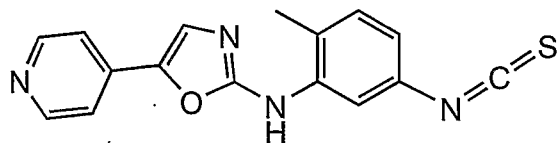


A solution of (2-methyl-5-nitro-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine (1 g, 3.39
15 mmol) in ethanol (50 mL) was treated with 10% Pd/C (120 mg) and hydrazine hydrate (3.50 mL, 112.5 mmol) was added drop wise over 10 min. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 2 h. The hot solution was filtered through a short pad of Celite, and the catalyst was washed with hot ethanol. The filtrates were concentrated under reduced vacuum to give the crude product. This
20 was silica gel column chromatographed (dichloromethane/ethanol : 97/3). 720 mg (80%) of (2-methyl-5-amino-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine was obtained as pale yellow powder.

m p 158 °C

¹H NMR (DMSO-*d*⁶) δ = 2.14 (s, 3H) ; 4.96 (bs, 2H) ; 6.30 (dd, *J* = 8.1-2.1, 1H) ;
25 6.87 (d, *J* = 8.1, 1H) ; 7.04 (d, *J* = 2.1, 1H) ; 7.50 (d, *J* = 6.0, 2H) ; 8.58 (d, *J* = 6.0, 2H) ; 7.76 (s, 1H) ; 9.28 (s, 1H).

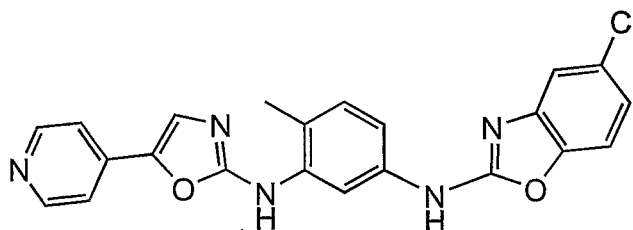
Preparation of (5-Isothiocyanto-2-methyl-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine



To a solution of (2-Methyl-5-amino-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine (500 mg, 1.88 mmol) in dichloromethane (70 mL) was added 1,1'-Thiocarbonyldi-2(1*H*)-pyridine (525 mg, 2.26 mmol). The mixture was stirred at room temperature overnight. After evaporation of the solvent under reduced pressure, the residue was silica gel column chromatographed (ethyl acetate/heptane : 50/50) to give 528 mg (91%) of the title compound as a beige solid.

¹H NMR (DMSO-*d*⁶) δ = 2.36 (s, 3H) ; 7.10 (dd, *J* = 8.1-2.1, 1H) ; 7.32 (d, *J* = 8.1, 1H) ; 7.56 (d, *J* = 6.0, 2H) ; 7.86 (s, 1H) ; 8.08 (d, *J* = 2.1, 1H) ; 8.62 (d, *J* = 6.0, 2H) ; 9.80 (s, 1H).

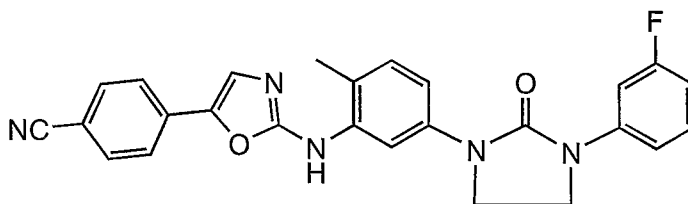
Preparation of *N*1-(5-Chloro-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine



To a solution of (5-Isothiocyanato-2-methyl-phenyl)-(5-pyridin-4-yl-oxazol-2-yl)-amine (120 mg, 0.39 mmol) in DMF (8 mL), was added 2-Amino-4-chloro-phenol (61 mg, 0.43 mmol). The mixture was stirred at room temperature overnight and yellow Mercury (II) oxide (72 mg, 0.39 mmol) was added. The mixture was stirred at room temperature 1h the precipitate was filtered through a short pad of Celite. The filtrate was concentrated under reduced vacuum to give the crude product. This was silica gel column chromatographed (dichloromethane/ethanol : 95/5) to give 112 mg (69%) of the title compound as a yellow solid.

^1H NMR ($\text{DMSO}-d^6$) δ = 2.26 (s, 3H) ; 7.14 (dd, J = 8.7-2.1, 1H) ; 7.22 (d, J = 8.7, 1H) ; 7.40 (d, J = 2.1, 1H) ; 7.47-7.53 (m, 4H) ; 7.79 (s, 1H) ; 8.12 (d, J = 2.1, 1H) ; 8.53 (s, 1H) ; 8.55 (s, 1H) ; 9.61 (s, 1H) ; 10.77 (s, 1H).

- 5 Preparation of 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile



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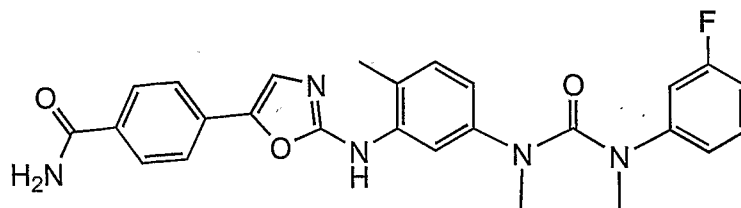
To a solution of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile (558 mg, 2 mmol) and chloroacetaldehyde (50 wt. % in water, 628 mg, 4 mmol) in acetonitrile (60 mL), was added at RT NaBH_3CN (253 mg, 4 mmol) and dropwise acetic acid (0.4 mL). The mixture was stirred at room temperature 1h. Ethyl acetate (50 mL) and saturated aqueous NaHCO_3 (50 mL) were added. The organic layer was washed with brine (20 mL), dried over MgSO_4 and concentrated to give a yellow solid. This was dissolved in toluene (40 mL) and treated with 1-Fluoro-3-isocyanato-benzene (274 mg, 2 mmol) at reflux for 2h. After evaporation of solvent under reduced vacuum, the crude product was dissolved in isopropanol (60 mL) and treated with potassium tert-butoxide (1.8 g, 16 mmol) at RT for 5 h. Water (20 mL) was added, the organic layer was separated dried over MgSO_4 and concentrated. The crude product was silica gel column chromatographed (dichloromethane/ethanol : 95/5) to give 408 mg (45%) of the title compound as a beige solid.

^1H NMR ($\text{DMSO}-d^6$) δ = 2.26 (s, 3H) ; 3.98 (s, 4H) ; 6.90 (t, J = 9.0, 1H) ; 7.20 (bs, 2H) ; 7.33-7.42 (m, 2H) ; 7.65-7.85 (m, 6H) ; 8.19 (s, 1H) ; 9.82 (s, 1H).

25

Preparation of 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile

30



Compound 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenyl amino}-oxazol-5-yl)-benzonitrile (30 mg, 0.066 mmol), was treated in EtOH (2 mL) with 3N NaOH (1 mL). The resulting mixture was stirred at reflux for 3h. After cooling to RT, 1N HCl was added until pH=6-7 and the precipitate filtered to give the title compound as a yellow solid (9 mg, 29%).

ES/MS : $m/z = 471$ $[M-H]^-$.

10 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.).

25 The cōmposition 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.

10 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.

25 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.

- 5 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.

10 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.

15 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.
20 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. Invest. 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.
25 L. and Scala, J., "The Percutaneous Absorption of Alkylmethyl Sulfides," Pharmacology of the Skin, Advances In Biology 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.,
30 "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 propellant 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 propellant 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
5 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 propellant 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
10 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.

15 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.

20 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
25 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
30 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.

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; diabete type II; 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.
- 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.
- 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

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 conditions 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*
5 *pneumoniae*, *Serratia marcescens*, *Citrobactor freundii* 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
10 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
15 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.

20

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
25 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
30 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 and Kinase domain 816) assay

Proliferation assays

Cells were washed two times in PBS before plating at 5×10^4 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 [^3H] thymidine (Amersham Life Science, UK) was added for 6 hours. Cells were harvested and filtered through glass fiber filters and [^3H] 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 mkit Δ 27 (juxtamembrane deletion), and
5 hkitD816V 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 a double point mutation (i.e. mutations JM-V560G and the kinase domain mutation
10 kitD816V), whereas the HMC1 subclone α 155 expresses only the mutation JM-V560G.

Immunoprecipitation assays and western blotting analysis

For each assay, 5.10⁶ 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
15 cells were stimulated with 250 ng / ml of rmKL. Cell lysates were immunoprecipitated with rabbit immunsera directed against the KIT cytoplasmic domain either with an anti murine KIT (Rottapel *et al.*, 1991) or an anti human KIT (Santa Cruz),. Western blot was hybridized either with the 4G10 anti-phosphotyrosine antibody (UBI) or with the appropriate rabbit immunsera anti KIT or with different
20 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).

25 • 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, c-Kit JMA27
30 and c-Kit D816V.

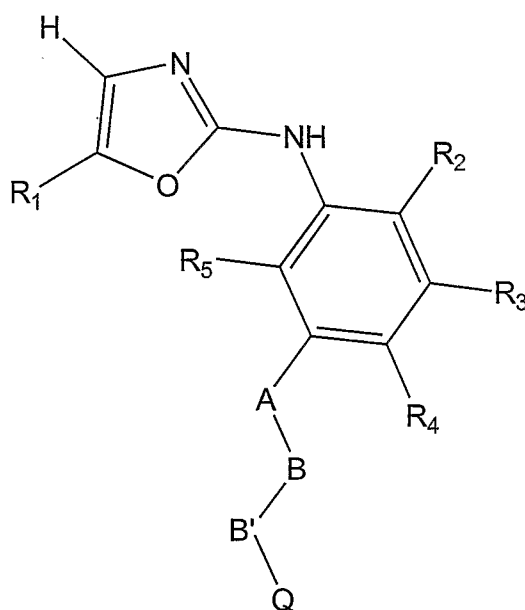
Target	IC ₅₀ (μM)	Compounds
c-Kit WT	IC ₅₀ < 1 μM	001 ; 002 ; 004 ; 011 ; 017 ; 021 ; 028 ; 030
c-Kit JM Δ27	IC ₅₀ < 1 μM	001 ; 017 ; 027 ; 028 ; 029 ; 030
c-Kit D816V	IC ₅₀ ≤ 1 μM	001 ; 002 ; 011 ; 017 ; 021 ; 030

CLAIMS

We claim:

5

1. A compound of formula I:



10

FORMULA I

Wherein substituents A, B, B', Q and R1 – R5 in Formula I are defined as follows:

A and B' is one of the following:

15 i) $(R_6)N(CH_2)_n$ where n is 0 or 1

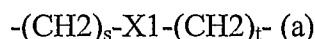
ii) $O(CH_2)_n$ where n is 0 or 1

iii) $S(CH_2)_n$ where n is 0 or 1

iv) $(CH_2)_n$ where n is 0, 1 or 2

v) $C(O)(CH_2)_n$ where n is 0 or 1

20 or when A and B' each are a nitrogen, they may be taken together to form a bivalent radical of formula :



where s and t each independently is 1 or 2 and X1 being O, S, NR10, N[C(=O)R10] or $(\text{CH}_2)_n$ where n is 0 or 1, and wherein each hydrogen in said formula (a) may be substituted with halo or C₁₋₄alkyl.

5

B is one of the following:

- i) (R6)N
 - ii) Oxygen
 - iii) S(O)_n where n is 0, 1 or 2
 - 10 iv) CH(R6)(R7)
 - v) C=δ, where δ is oxygen, sulfur, NH or N-CN
 - vi) C(R6)=C(R7)
 - vii) N=C(R6)
- 15 R6 and R7 each independently are hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₄haloalkyl, C₁₋₆alkoxy, C₁₋₄hydroxyalkyl.

R1 is selected from:

- i) hydrogen, halogen (selected from F, Cl, Br or I), or
- 20 ii) an alkyl¹ group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl, cyano, nitro, formyl; as well as CO-R, COO-R, CONH-R, SO₂-R, and
- 25 SO₂NH-R wherein R is a linear or branched alkyl group containing 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality ; as well as a cycloalkyl or aryl¹ or heteroaryl¹ group optionally substituted by a pendant basic nitrogen functionality, or

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

- halogen(selected from I, F, Cl or Br);
- an alkyl¹ group;
- 5 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- 10 - NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl, or

iv) a heteroaryl¹ group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl ,
15 triazolyl, tetrazolyl, indolyl, benzimidazole, benzoxazole, benzothiazole, 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 alkyl¹ group;
- 20 - a cycloalkyl, aryl or heteroaryl group optionally substituted by a pendant basic nitrogen functionality,
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- 25 - NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, or

v) an O-aryl¹, or NH-aryl¹, or O-heteroaryl¹ or NH-heteroaryl¹ group

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

vi) NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl or heteroaryl.

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

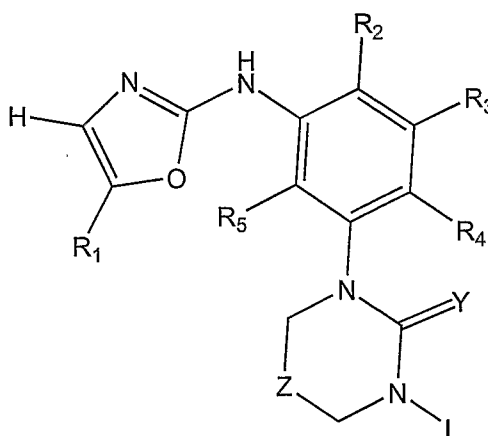
15

Q is selected from:

- i) Alkyl¹
- ii) Aryl¹
- iii) Heteroaryl¹

20

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

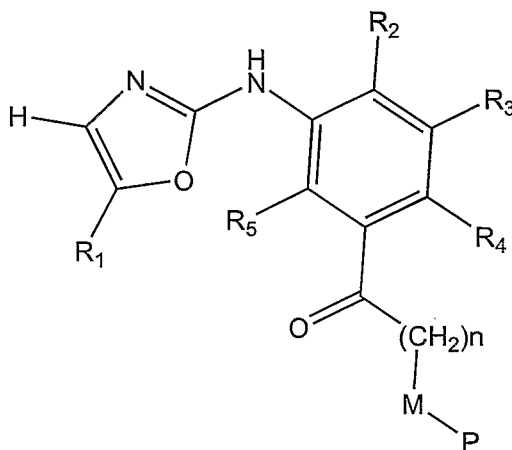


FORMULA II

- 5 Wherein Y is oxygen, sulfur, NH or N-CN, Z is oxygen, sulfur, N(R6) or (CH₂)_n where n is 0, 1 or 2, L is selected from Alkyl¹, Aryl¹ or Heteroaryl¹ and R1, R2, R3, R4, R5 and R6 as defined in claim 1.

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

10

**FORMULA III**

15

Wherein

n is an integer of 0, 1 or 2.

M is oxygen, sulfur or (CH₂)_n where n is 0, 1 or 2.

P is selected from N(R8)(R9), Alkyl¹, Aryl¹ or Heteroaryl¹.

- 20 R8 and R9 each independently is hydrogen, Alkyl¹, Aryl¹ or Heteroaryl¹.

R8 and R9 may be taken together to form a bivalent radical of formula :

-(CH₂)_v-X₂-(CH₂)_w- (b)

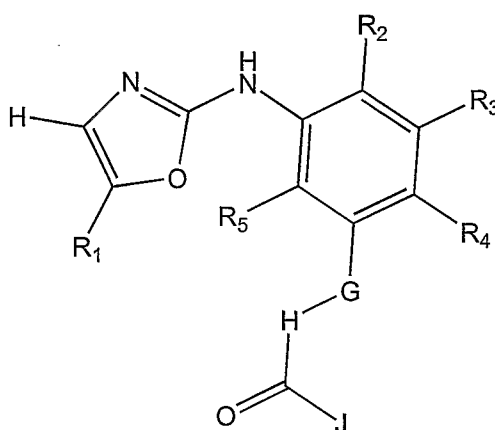
where v and w each independently is 1 or 2 and X₂ being CH₂, O, S, NR₁₀ or N[C(=O)R₁₀] and wherein each hydrogen in said formula (b) may be substituted with

- 25 halo or C₁₋₄alkyl.

R10 is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₄haloalkyl, C₁₋₆alkoxy, C₁₋₄hydroxyalkyl.

R1, R2, R3, R4 and R5 have the meaning described above.

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



10

FORMULA IV

Wherein

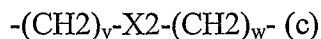
G is oxygen, sulfur, N(R11) or (CH₂)_n where n is 1 or 2.

H is oxygen, N(R11) or (CH₂)_n where n is 1 or 2.

- 15 J is selected from N(R12)(R13), Alkyl¹, Aryl¹ or Heteroaryl¹.

R12 and R13 each independently is hydrogen, Alkyl¹, Aryl¹ or Heteroaryl¹.

R12 and R13 may be taken together to form a bivalent radical of formula :



where v and w each independently is 1 or 2 and X₂ being CH₂, O, S, NR₁₄ or

- 20 N[C(=O)R₁₄] and wherein each hydrogen in said formula (c) may be substituted with halo or C₁₋₄alkyl.

R₁₁ and R₁₄ each independently is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₄haloalkyl, C₁₋₆alkoxy, C₁₋₄hydroxyalkyl.

R1, R2, R3, R4 and R5 have the meaning described above.

25

5. A compound as claimed in claim 1 selected from:

- *N*-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-*C*-phenyl-methane sulfonamide
- 5 • 4-{2-[5-(Benzooxazol-2-ylamino)-2-methyl-phenylamino]-oxazol-5-yl}-benzonitrile
- 4-{2-[5-(Benzooxazol-2-ylamino)-2-methyl-phenylamino]-oxazol-5-yl}-benzonitrile
- 4-{2-[5-(Benzothiazol-2-ylamino)-2-methyl-phenylamino]-oxazol-5-yl}-benzonitrile
- *N*1-Benzooxazol-2-yl-4-methyl-*N*3-(5-pyridin-3-yl-oxazol-2-yl)-benzene-1,3-diamine
- 10 • *N*1-(5-Chloro-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- *N*1-(6-Chloro-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- *N*1-(5-Ethanesulfonyl-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- 15 • 4-Methyl-*N*1-(5-methyl-benzooxazol-2-yl)-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- *N*1-(5-Fluoro-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- 20 • *N*1-(6-Fluoro-benzooxazol-2-yl)-4-methyl-*N*3-(5-pyridin-4-yl-oxazol-2-yl)-benzene-1,3-diamine
- 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile
- 4-(2-{5-[3-(3-cyano-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile
- 25 • 4-(2-{5-[3-(3-Fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-2-methyl-phenylamino}-oxazol-5-yl)-benzamide
- 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-imidazolidin-2-one

- 1-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-3-(3-trifluoromethyl-phenyl)-imidazolidin-2-one
- 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-tetrahydro-pyrimidin-2-one
- 5 • 1-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-3-phenyl-propan-1-one
- 4-[2-(5-Acetyl-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile
- 4-(2-{5-[3-(4-Fluoro-phenyl)-propionyl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile
- 4-{2-[2-Methyl-5-(3-phenyl-propionyl)-phenylamino]-oxazol-5-yl}-benzonitrile
- 10 • 4-(2-{5-[3-(3-Fluoro-phenyl)-propionyl]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile
- 4-[2-(5-Acetyl-2-methyl-phenylamino)-oxazol-5-yl]-benzamide
- 1-(4-Fluoro-phenyl)-2-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenylamino]-ethanone
- 15 • 1-(4-Fluoro-phenyl)-2-{methyl-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amino}-ethanone
- 4-({Methyl-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amino}-acetyl)-benzonitrile
- 2-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenylamino]-1-phenyl-ethanone
- 20 • 4-(2-{5-[2-(4-Fluoro-phenyl)-2-oxo-ethylamino]-2-methyl-phenylamino}-oxazol-5-yl)-benzonitrile
- 4-(2-{5-[2-(4-Cyano-phenyl)-2-oxo-ethylamino]-2-chloro-phenylamino}-oxazol-5-yl)-benzonitrile
- N-[4-Methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-benzyl]-benzamide
- 25 • 2-{Methyl-[4-methyl-3-(5-pyridin-4-yl-oxazol-2-ylamino)-phenyl]-amino}-1-phenyl-ethanone

6. A compound according to one of claims 1 to 4, wherein R1 is pyridyl or benzonitril which may additionally bear any combination, at any one ring position, of one or more substituents such as

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- hydrogen;
- halogen (selected from F, Cl, Br or I);
- an alkyl¹ group;
- an aryl¹ group;
- 5 - trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHCO-R or NHCOO-R or NHCONH-R or NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or CONH-R or SO₂-R or SO₂NH-R wherein R
- 10 corresponds to hydrogen, alkyl¹ or aryl¹ group.

7. A pharmaceutical composition comprising a compound according to one of claims 1 to 6.

- 15 8. A pharmaceutical composition according to claim 7 comprising a pharmaceutically acceptable carrier suitable for oral or topical administration.

9. A pharmaceutical composition according to claim 7 formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, and suspensions.

20

10. A cosmetic composition for topical administration comprising a compound according to one of claims 1 to 6.

11. Use of a compound according to one of claims 1 to 6 to manufacture a
- 25 medicament.

12. Use according to claim 11 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
- 30 cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic

syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas.

13. Use according to claim 11 to manufacture a medicament for treating allergic
5 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.

10 14. Use according to claim 11 to manufacture a medicament for treating inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

15 15. Use according to claim 11 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.

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16. Use according to claim 11 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.

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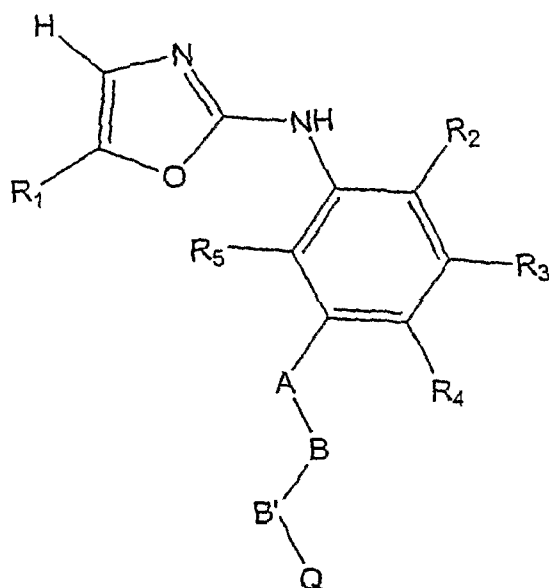
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
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[Continued on next page]

(54) Title: SUBSTITUTED OXAZOLE DERIVATIVES AND THEIR USE AS TYROSINE KINASE INHIBITORS



(I)

(57) Abstract: The present invention relates to novel compounds selected from substituted oxazole derivatives of formula (I) 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. More particularly, these compounds are potent and selective c-kit, bcr-abl and Fit-3 inhibitors.



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23 November 2006

INTERNATIONAL SEARCH REPORT

International application No

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C07D413/12 C07D413/14 C07D417/12 A61P29/00 A61P35/00
A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/040139 A (AB SCIENCE; CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE ; INSTITUT CU) 6 May 2005 (2005-05-06) abstract; claim 1 examples	1-16
X	WO 03/062215 A (KYLIX PHARMACEUTICALS B.V; STIEBER, FRANK; HELLMUTH, KLAUS; WALDMANN,) 31 July 2003 (2003-07-31) the whole document	1-16
X	WO 2004/032882 A (SMITHKLINE BEECHAM CORPORATION; BROWN, MATTHEW, LEE; CHEUNG, MUI; DICK) 22 April 2004 (2004-04-22) claim 1 examples	1-16
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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/001059 A (BRISTOL-MYERS SQUIBB COMPANY; BORZILLERI, ROBERT, M; TOKARSKI, JOHN, S) 31 December 2003 (2003-12-31) the whole document -----	1-16
X	WO 2005/000298 A (TRIAD THERAPEUTICS, INC; DONG, QING; PIERRE, FABRICE; WANG, JIANQIANG) 6 January 2005 (2005-01-06) claim 1 examples -----	1-16
X	HARRIS ET AL.: "Discovery and evaluation of 2-anilino-5-aryloxazoles as a novel class of VEGFR2 kinase inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, 2005, pages 1610-1619, XP002398446 tables 1-3 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/001249

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2005040139	A	06-05-2005	AU	2004283162 A1		06-05-2005
			CA	2542909 A1		06-05-2005
			EP	1684750 A2		02-08-2006
WO 03062215	A	31-07-2003	CA	2474322 A1		31-07-2003
WO 2004032882	A	22-04-2004	AU	2003287178 A1		04-05-2004
			EP	1551813 A2		13-07-2005
			JP	2006503081 T		26-01-2006
WO 2004001059	A	31-12-2003	AU	2003251559 A1		06-01-2004
			EP	1513818 A2		16-03-2005
			JP	2005533808 T		10-11-2005
WO 2005000298	A	06-01-2005	AU	2004251668 A1		06-01-2005
			BR	PI0410905 A		27-06-2006
			CA	2528438 A1		06-01-2005
			EP	1635824 A2		22-03-2006
			MX	PA05013075 A		17-03-2006

15 If available, please enter the **Chinese abstract** text in the space below.

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