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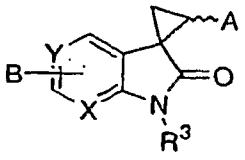
(54) Title: 3-SPIR0CYCL0PR0PYL2-0XIND0LE KINASE INHIBITORS



(I)

(57) Abstract: The present invention relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Formula: (I).

3-SPIROCYCLOPROPYL2-OXINDOLE KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is based on, and claims the benefit of, U.S. Provisional Application No. 60/699,073, filed July 13, 2005, and which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field Of The Invention

The present invention relates to novel compounds capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction. The present invention is also directed to methods of regulating, modulating or inhibiting tyrosine kinases, whether of the receptor or non-receptor class, for the prevention and/or treatment of disorders related to unregulated tyrosine kinase signal transduction, including cell growth, metabolic, and blood vessel proliferative disorders.

2. Description Of The Related Art

Protein tyrosine kinases (PTKs) comprise a large and diverse class of proteins having enzymatic activity. The PTKs play an important role in the control of cell growth and differentiation.

For example, receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate

cellular response (e.g., cell division, metabolic homeostasis, and responses to the extracellular microenvironment).

With respect to receptor tyrosine kinases, it has been shown also that tyrosine phosphorylation sites function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Several intracellular substrate proteins that associate with receptor tyrosine kinases (RTKs) have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain but serve as adapters and associate with catalytically active molecules. The specificity of the interactions between receptors or proteins and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. These observations suggest that the function of each receptor tyrosine kinase is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

Aberrant expression or mutations in the PTKs have been shown to lead to either uncontrolled cell proliferation (e.g. malignant tumor growth) or to defects in key developmental processes. Consequently, the biomedical community has expended significant resources to discover the specific biological role of members of the PTK family, their function in differentiation processes, their involvement in tumorigenesis and in other diseases, the biochemical mechanisms underlying their signal transduction pathways activated upon ligand stimulation and the development of novel drugs.

Tyrosine kinases can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular).

The RTKs comprise a large family of transmembrane receptors with diverse biological activities. The intrinsic function of RTKs is activated upon ligand binding, which results in phophorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses.

At present, at least nineteen (19) distinct RTK subfamilies have been identified. One RTK subfamily, designated the HER subfamily, is believed to be comprised of EGFR, HER2, HER3 and HER4. Ligands to the Her subfamily of receptors include epithelial growth factor (EGF), TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin.

A second family of RTKs, designated the insulin subfamily, is comprised of the INS-R, the IGF-1R and the IR-R. A third family, the "PDGF" subfamily includes the PDGF α and β receptors, CSFIR, c-kit and FLK-II. Another subfamily of RTKs, identified as the FLK family, is believed to be comprised of the Kinase insert Domain-Receptor fetal liver kinase-1 (KDR/FLK-1), the fetal liver kinase 4 (FLK-4) and the fms-like tyrosine kinase 1 (flt-1). Each of these receptors was initially believed to be receptors for hematopoietic growth factors. Two other subfamilies of RTKs have been designated as the FGF receptor family (FGFR1, FGFR2, FGFR3 and FGFR4) and the Met subfamily (c-met and Ron).

Because of the similarities between the PDGF and FLK subfamilies, the two subfamilies are often considered together. The known RTK subfamilies are identified in Plowman et al, 1994, DN&P 7(6): 334-339, which is incorporated herein by reference.

The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor tyrosine kinases, comprising eleven (11) subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been

identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs and include Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, 1993, Oncogen 8: 2025-2031, which is incorporated herein by reference.

Many of the tyrosine kinases, whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways leading to cellular signal cascades leading to pathogenic conditions, including cancer, psoriasis and hyper immune response.

In view of the surmised importance of PTKs to the control, regulation and modulation of cell proliferation the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands soluble receptors and antibodies RNA ligands and tyrosine kinase inhibitors.

More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds, vinylene-azaindole derivatives and 1-cyclopropyl-4-pyridyl-quinolones have been described generally as tyrosine kinase inhibitors. Styryl compounds, styryl-substituted pyridyl compounds certain quinazoline derivatives seleoindoles and selenides, tricyclic polyhydroxylic compounds and benzylphosphonic acid compounds have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer.

The identification of effective small compounds which specifically inhibit signal transduction by modulating the activity of receptor and non-receptor tyrosine kinases to regulate and modulate abnormal or inappropriate cell proliferation is therefore desirable and one object of this invention.

Finally, certain small compounds are disclosed in U.S. Patents 5,792,783; 5,834,504; 5,883,113; 5,883,116 and 5,886,020 as useful for the treatment of

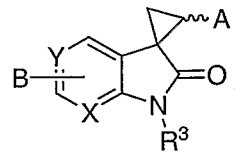
diseases related to unregulated TKS transduction. See also, U.S. Patents 6,541,504; 6,559,173; 6,765,012; 6,747,025; 6,699,863; 7,005,444; 7,015,220 and 7,060,844 . These patents are hereby incorporated by reference in its entirety for the purpose of disclosing starting materials and methods for the preparation thereof, screens and assays to determine a claimed compound's ability to modulate, regulate and/or inhibit cell proliferation, indications which are treatable with said compounds, formulations and routes of administration, effective dosages, etc.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to organic molecules capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction. Such compounds are useful for the treatment of diseases related to unregulated TKS transduction, including cell proliferative diseases such as cancer, atherosclerosis, restenosis, metabolic diseases such as diabetes, inflammatory diseases such as psoriasis and chronic obstructive pulmonary disease, vascular proliferative disorders such as diabetic retinopathy, age-related macular degeneration and retinopathy of prematurity, autoimmune diseases and transplant rejection.

DETAILED DESCRIPTION OF THE INVENTION

The VEGFR inhibitors, i.e. the compounds of the present invention, are as shown in Formula I, below.

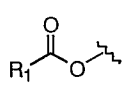
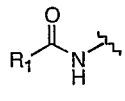
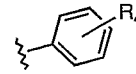
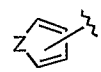
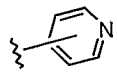


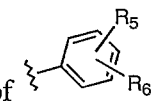
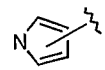
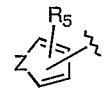
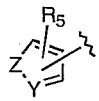
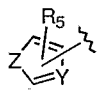
Formula I

wherein:

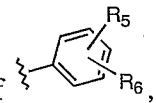
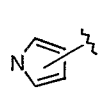
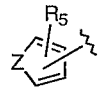
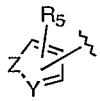
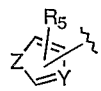
X is C or N;

Y is C or N;

B is selected from the group consisting of H, halogen, hydroxy, amino, lower alkyl, R^1-O, or R^1-NH, alkylSO$_2$NH-,  ,  ,  ,  ,  ,  and  , with the proviso that if X is N, B is not bonded to X and if Y is N, B is not bonded to Y;

A is selected from the group consisting of  ,  ,  ,  and  ;

Z is selected from the group consisting of NH, S and O;

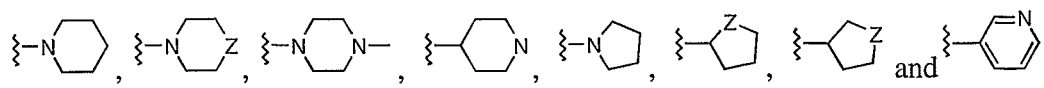
R^1 is H, or lower alkyl or may be selected from the group consisting of  ,  ,  ,  and  ;

R^3 is selected from the group consisting of H, lower alkyl and -CH_2-N(-CH_2CH_2W CH_2CH_2-);

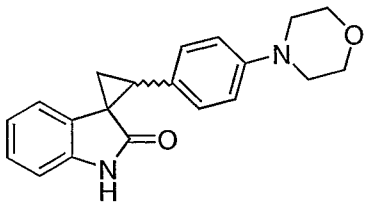
R^4 is selected from the group consisting of H, OR^1, NR^1, halogen and hydroxyl;

W is selected from the group consisting of Z, SO_2, or CH_2;

R^5 and R^6 are independently selected from the group consisting of H, halogen, hydroxy, R^1-O, NR^1, lower alkyl, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1, wherein n is 0-4 and R^2 is H, or lower alkyl; and

Het is a heterocyclic radical selected from the group consisting of  .

Preferred are the compounds shown below: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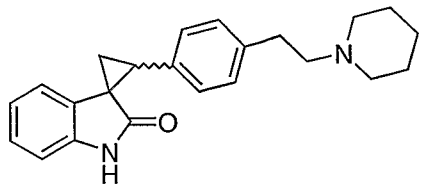
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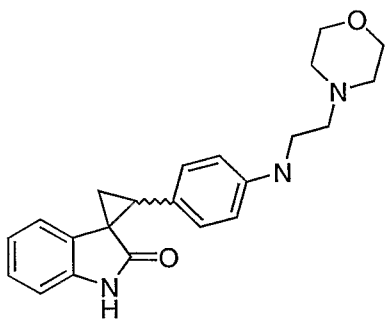
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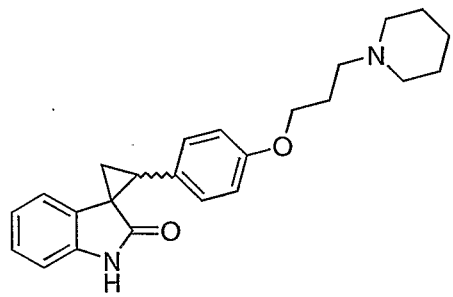
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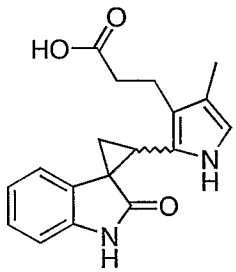
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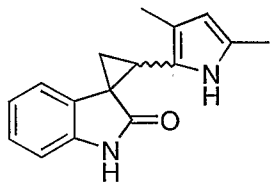
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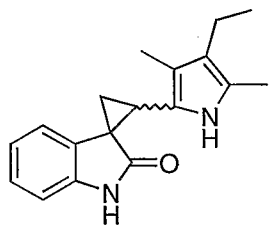
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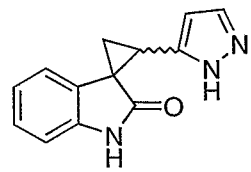
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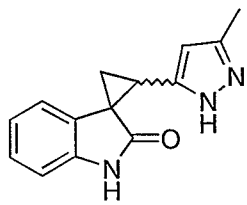
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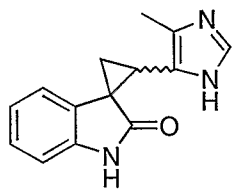
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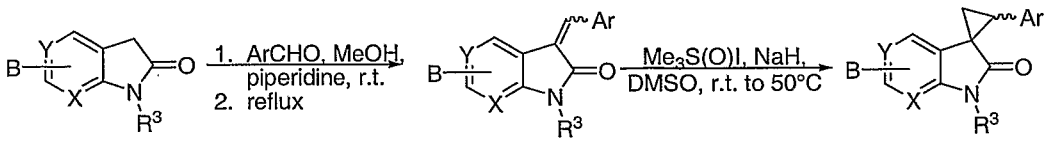
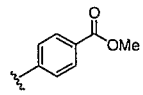
These compounds may be prepared by the general method, wherein Ar is A in Formula I



In one specific example of preparing the compounds of this invention by the general method, wherein

$B = X = Y = R_3 = H$ and Ar =  the first step results in an 81% yield.

The present invention is further directed to pharmaceutical compositions comprising a pharmaceutically effective amount of the above-described compounds and a pharmaceutically acceptable carrier or excipient. Such a composition is believed to modulate signal transduction by a tyrosine kinase, either by inhibition of catalytic activity, affinity to ATP or ability to interact with a substrate.

More particularly, the compositions of the present invention may be included in methods for treating diseases comprising proliferation, fibrotic or metabolic disorders, for example cancer, fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy.

The following defined terms may be used throughout this specification:

"Me" refers to methyl.

"Et" refers to ethyl.

"tBu" refers to t-butyl.

"iPr" refers to i-propyl.

"Ph" refers to phenyl.

"Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric

acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Alkyl" refers to a straight-chain, branched or cyclic saturated aliphatic hydrocarbon. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. Typical alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl and the like. The alkyl group may be optionally substituted with one or more substituents are selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Alkenyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon group containing at least one carbon-carbon double bond. Preferably, the alkenyl group has 1 to 12 carbons. More preferably it is a lower alkenyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Alkynyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon containing at least one carbon-carbon triple bond. Preferably, the alkynyl group has 1 to 12 carbons. More preferably it is a lower alkynyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. The alkynyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Alkoxyl" refers to an "O-alkyl" group.

"Aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups. The aryl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, OH, NO_2, amine, thioether, cyano, alkoxy, alkyl, and amino.

"Alkaryl" refers to an alkyl that is covalently joined to an aryl group. Preferably, the alkyl is a lower alkyl.

"Carbocyclic aryl" refers to an aryl group wherein the ring atoms are carbon.

"Heterocyclic aryl" refers to an aryl group having from 1 to 3 heteroatoms as ring atoms, the remainder of the ring atoms being carbon. Heteroatoms include oxygen, sulfur, and nitrogen. Thus, heterocyclic aryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like.

"Hydrocarbyl" refers to a hydrocarbon radical having only carbon and hydrogen atoms. Preferably, the hydrocarbyl radical has from 1 to 20 carbon atoms, more preferably from 1 to 12 carbon atoms and most preferably from 1 to 7 carbon atoms.

"Substituted hydrocarbyl" refers to a hydrocarbyl radical wherein one or more, but not all, of the hydrogen and/or the carbon atoms are replaced by a halogen, nitrogen, oxygen, sulfur or phosphorus atom or a radical including a halogen, nitrogen, oxygen, sulfur or phosphorus atom, e.g. fluoro, chloro, cyano, nitro, hydroxyl, phosphate, thiol, etc.

"Amide" refers to -C(O)-NH-R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Thioamide" refers to -C(S)-NH-R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Amine" refers to a -N(R'')R''' group, wherein R'' and R''' are independently selected from the group consisting of alkyl, aryl, and alkylaryl.

"Thioether" refers to -S-R'', wherein R'' is alkyl, aryl, or alkylaryl.

"Sulfonyl" refers to -$S(O)_2$-R'''', where R'''' is aryl, C(CN)=C-aryl, CH_2CN, alkyaryl, sulfonamide, NH-alkyl, NH-alkylaryl, or NH-aryl.

The present invention relates to compounds capable of regulating and/or modulating tyrosine kinase signal transduction and more particularly receptor and non-receptor tyrosine kinase signal transduction.

Receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects and responses to the extracellular microenvironment).

It has been shown that tyrosine phosphorylation sites in growth factor receptors function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Several intracellular substrate proteins that associate with receptor tyrosine kinases have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain but serve as adapters and associate with catalytically active molecules. The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. These observations suggest that the function of each receptor tyrosine kinase is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the

selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

Tyrosine kinase signal transduction results in, among other responses, cell proliferation, differentiation and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis, e.g. macular degeneration).

This invention is therefore directed to compounds which regulate, modulate and/or inhibit tyrosine kinase signal transduction by affecting the enzymatic activity of the RTKs and/or the non-receptor tyrosine kinases and interfering with the signal transduced by such proteins. More particularly, the present invention is directed to compounds which regulate, modulate and/or inhibit the RTK and/or non-receptor tyrosine kinase mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including but not limited to carcinoma, sarcoma, leukemia, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers and bone cancers.

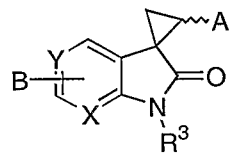
All references cited herein are hereby incorporated by reference in their entirety.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same

result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof.

Claims:

1. A novel compound selected from the group consisting of compounds represented by the general formula:

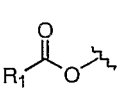
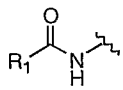
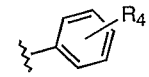
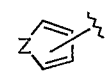
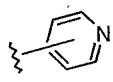


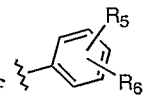
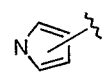
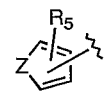
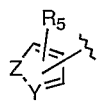
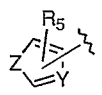
Formula I

wherein:

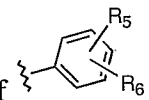
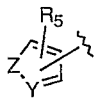
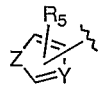
X is C or N;

Y is C or N;

B is selected from the group consisting of H, halogen, hydroxy, amino, lower alkyl, R^1-O, or R^1-NH, alkylSO_2NH-,  ,  ,  ,  ,  ,  and  , with the proviso that if X is N, B is not bonded to X and if Y is N, B is not bonded to Y;

A is selected from the group consisting of  ,  ,  ,  and  ;

Z is selected from the group consisting of NH, S and O;

R^1 is H, or lower alkyl or may be selected from the group consisting of  ,  ,  ,  and  ;

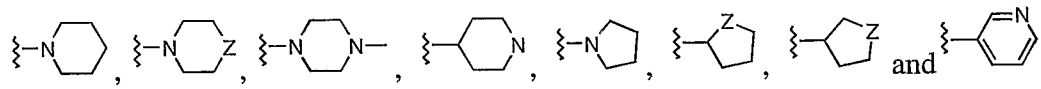
R^3 is selected from the group consisting of H, lower alkyl and -CH_2-N(-CH_2CH_2W CH_2CH_2-);

R^4 is selected from the group consisting of H, OR^1, NR^1, halogen and hydroxyl;

W is selected from the group consisting of Z, SO_2, or CH_2 ;

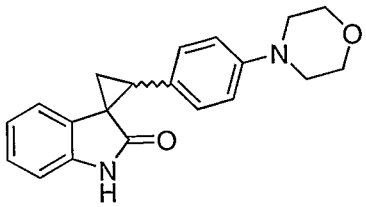
R^5 and R^6 are independently selected from the group consisting of H, halogen, hydroxy, R^1-O, NR^1, lower alkyl, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1, wherein n is 0-4 and R^2 is H, or lower alkyl; and

Het is a heterocyclic radical selected from the group consisting of



and

2. The compound of claim 1 wherein said compound is selected from the group consisting of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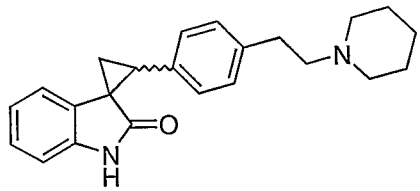
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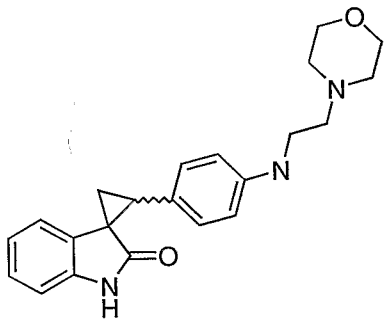
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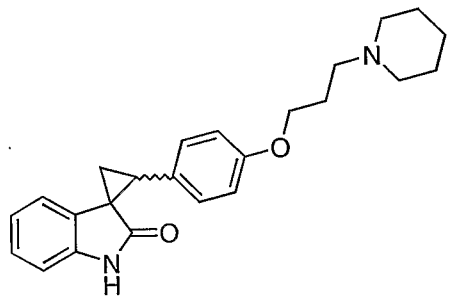
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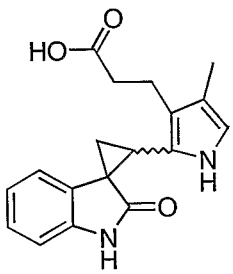
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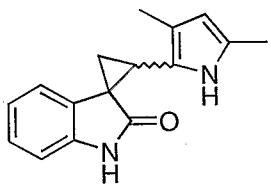
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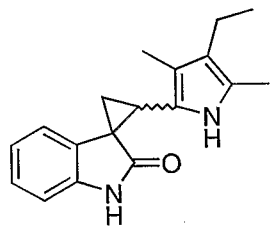
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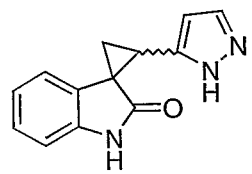
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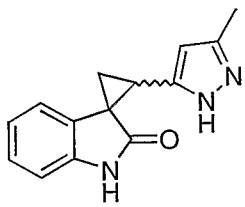
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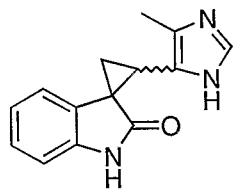

.

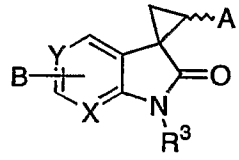
3. A method for treating diseases related to unregulated tyrosine kinase signal
10 transduction, wherein said disease is selected from the group consisting of

carcinoma, sarcoma, leukemia, erythromblastoma, glioblastoma, meningioma, astrocytoma, melanoma, myoblastoma, brain cancer, bladder cancer, ovarian cancer, gastric cancer, pancreas cancer, colon cancer, blood cancer, lung cancer, bone cancer, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, arthritis and restenosis, hepatic cirrhosis, atherosclerosis and surgical adhesions.glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies, psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative diseases the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

4. The method of claim 3, wherein said compound is a compound of claim 2.

AMENDED CLAIMS
received by the International Bureau on 01 December 2006 (01.02.2006)

1. A novel compound selected from the group consisting of compounds represented by the general formula:

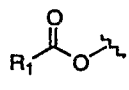
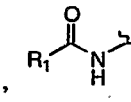
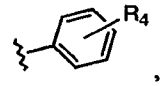
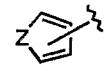
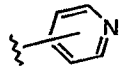


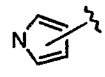
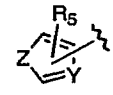
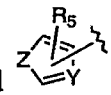
Formula I

wherein:

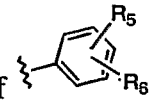
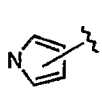
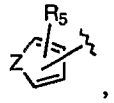
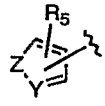
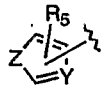
X is C or N;

Y is C or N; .

B is selected from the group consisting of H, halogen, hydroxy, amino, lower alkyl, R^1-O, or R^1-NH, alkylSO_2NH-,  ,  ,  ,  ,  ,  and  , with the proviso that if X is N, B is not bonded to X and if Y is N, B is not bonded to Y;

A is selected from the group consisting of,  ,  , and  ;

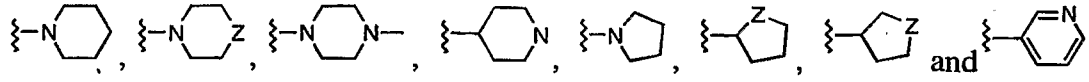
Z is selected from the group consisting of NH, S and O;

R^1 is H, or lower alkyl or may be selected from the group consisting of  ,  ,  ,  and  ;

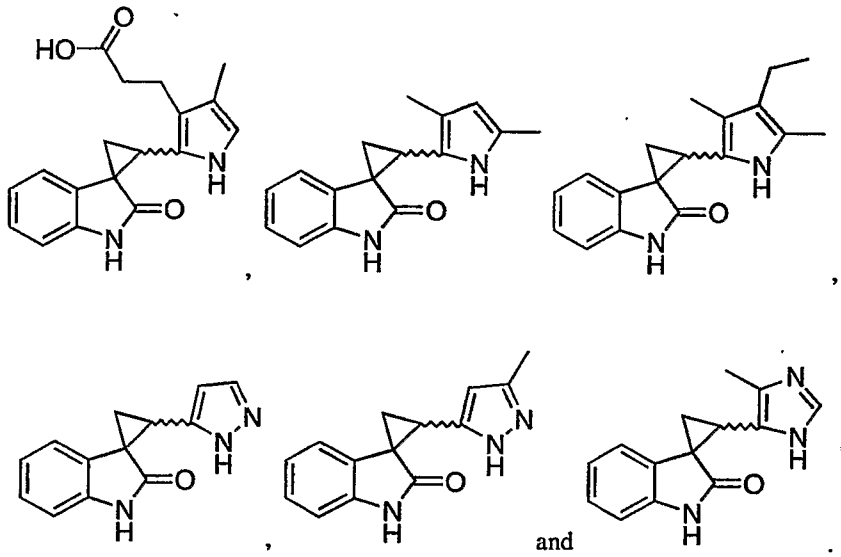
R^3 is selected from the group consisting of H, lower alkyl and -CH_2-N(-CH_2CH_2W CH_2CH_2-);

R^4 is selected from the group consisting of H, OR^1, NR^1, halogen and hydroxyl;

W is selected from the group consisting of Z, SO_2, or CH_2;
R^5 and R^6 are independently selected from the group consisting of H, halogen, hydroxy, R^1-O, NR^1, lower alkyl, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1, wherein n is 0-4 and R^2 is H, or lower alkyl; and
Het is a heterocyclic radical selected from the group consisting of

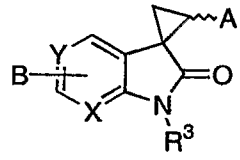


2. The compound of claim 1 wherein said compound is selected from the group consisting of



3. A method for treating diseases related to unregulated tyrosine kinase signal transduction, wherein said disease is selected from the group consisting of carcinoma, sarcoma, leukemia, erythromblastoma, glioblastoma, meningioma, astrocytoma, melanoma, myoblastoma, brain cancer, bladder cancer, ovarian cancer, gastric cancer, pancreas cancer, colon cancer, blood cancer, lung cancer, bone cancer, diabetic retinopathy, age-related macular degeneration, retinopathy of

prematurity, arthritis and restenosis, hepatic cirrhosis, atherosclerosis and surgical adhesions.glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies, psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative diseases the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound selected from the group consisting of compounds represented by the general formula:

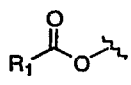
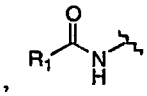
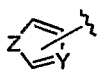


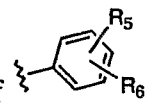
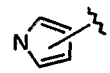
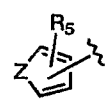
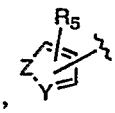
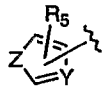
Formula I

wherein:

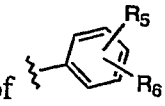
X is C or N;

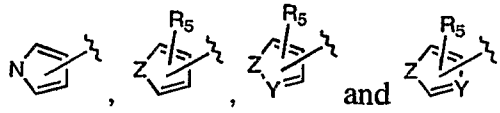
Y is C or N;

B is selected from the group consisting of H, halogen, hydroxy, amino, lower alkyl, R^1-O, or R^1-NH, alkylSO_2NH-,  ,  ,  ,  ,  ,  and  , with the proviso that if X is N, B is not bonded to X and if Y is N, B is not bonded to Y;

A is selected from the group consisting of  ,  ,  ,  and  ;

Z is selected from the group consisting of NH, S and O;

R^1 is H, or lower alkyl or may be selected from the group consisting of  ,



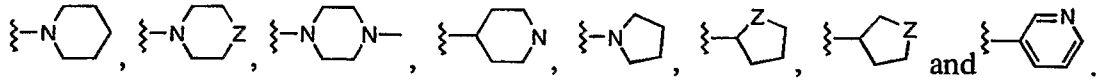
R^3 is selected from the group consisting of H, lower alkyl and -CH_2-N(-CH_2CH_2W CH_2CH_2-);

R^4 is selected from the group consisting of H, OR^1, NR^1, halogen and hydroxyl;

W is selected from the group consisting of Z, SO_2, or CH_2;

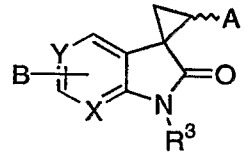
R^5 and R^6 are independently selected from the group consisting of H, halogen, hydroxy, R^1-O, NR^1, lower alkyl, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1, wherein n is 0-4 and R^2 is H, or lower alkyl; and

Het is a heterocyclic radical selected from the group consisting of



4. The method of claim 3, wherein said compound is a compound of claim 2 or claim 6.

5. A novel compound selected from the group consisting of compounds represented by the general formula:

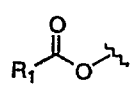
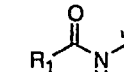
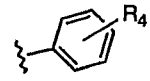
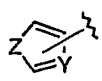


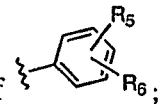
Formula I

wherein:

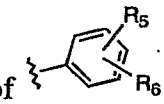
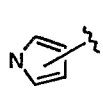
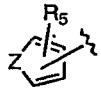
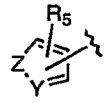
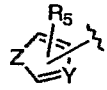
X is C or N;

Y is C or N;

B is selected from the group consisting of H, halogen, hydroxy, amino, lower alkyl, R^1-O, or R^1-NH, alkylSO_2NH-,  ,  ,  ,  ,  ,  and  , with the proviso that if X is N, B is not bonded to X and if Y is N, B is not bonded to Y;

A is selected from the group consisting of  ;

Z is selected from the group consisting of NH, S and O;

R^1 is H, or lower alkyl or may be selected from the group consisting of  ,  ,  ,  and  ;

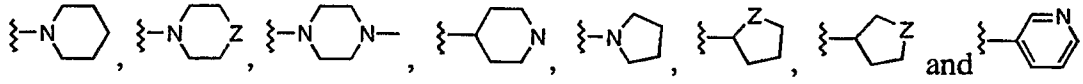
R^3 is selected from the group consisting of H, lower alkyl and -CH_2-N(-CH_2CH_2W CH_2CH_2-);

R^4 is selected from the group consisting of H, OR^1, NR^1, halogen and hydroxyl;

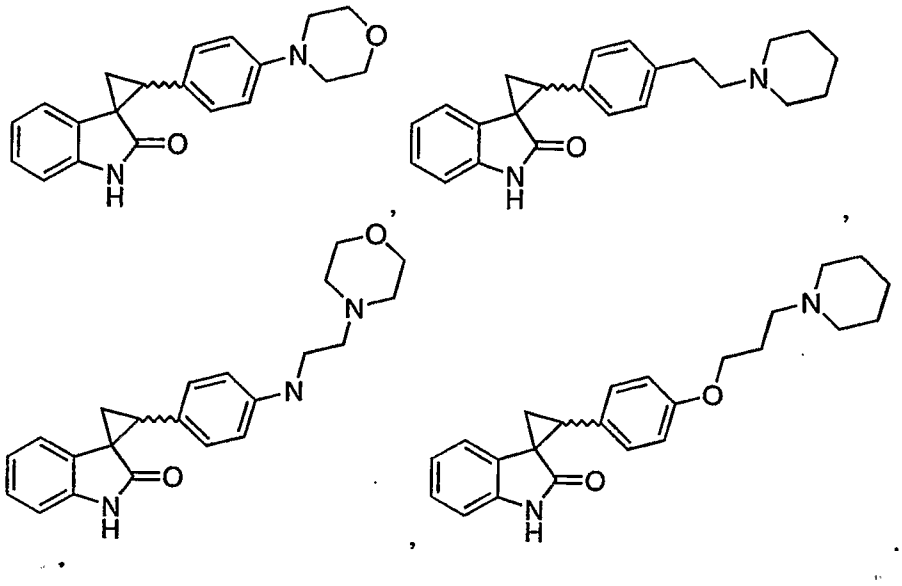
W is selected from the group consisting of Z, SO_2, or CH_2;

R^5 is selected from the group consisting of H, halogen, hydroxy, R^1-O, NR^1, lower alkyl, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1; R^6 is selected from the group consisting of halogen, hydroxy, R^1-O, NR^1, lower alkyl, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1 n is 0 to 4; and R^2 is H, or lower alkyl; and

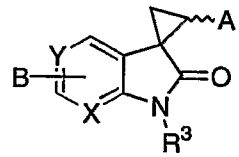
Het is a heterocyclic radical selected from the group consisting of

 .

6. The compound of claim 5 wherein said compound is selected from the group consisting of



7. A novel compound selected from the group consisting of compounds represented by the general formula:

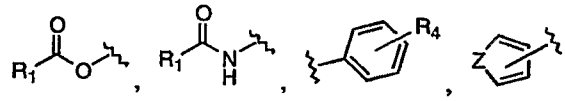
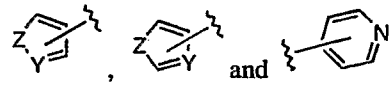


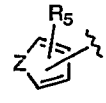
Formula I

wherein:

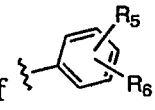
X is C or N;

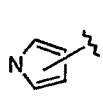
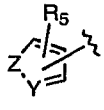
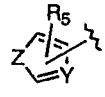
Y is C or N;

B is selected from the group consisting of H, halogen, hydroxy, amino, lower alkyl, R^1-O, or R^1-NH, alkylSO_2NH-,  and  , with the proviso that if X is N, B is not bonded to X and if Y is N, B is not bonded to Y;

A is selected from the group consisting of  ;

Z is selected from the group consisting of NH, S and O;

R^1 is H, or lower alkyl or may be selected from the group consisting of  ,

 ,  ,  and  ;

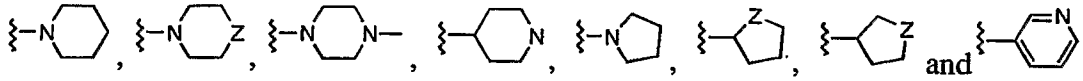
R^3 is selected from the group consisting of H, lower alkyl and $-CH_2-N(-CH_2CH_2W CH_2CH_2-)$;

R^4 is selected from the group consisting of H, OR^1, NR^1, halogen and hydroxyl;

W is selected from the group consisting of Z, SO_2, or CH_2;

R^5 is independently selected from the group consisting of hydroxy, R^1-O, NR^1, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1; R^6 is selected from the group consisting of H, hydroxy, R^1-O, NR^1, -W-$(CH_2)_n$-Het, –W-$(CH_2)_n$-NR^1R^2 and -W-$(CH_2)_n$-CO_2R^1; n is 0 to 4; R^2 is H, or lower alkyl; and

Het is a heterocyclic radical selected from the group consisting of

 .

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/026521

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/96 C07D403/04 A61K31/404 A61P35/00

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 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/037247 A (IRM LLC [US]; SCRIPPS RESEARCH INST [US]; HE YUN [US]; JIANG TAO [US];) 6 May 2004 (2004-05-06) compounds 35, 36, 38-40, 49, 55, 57, 59, 61, 64, 65, 67	1
A	US 5 792 783 A (TANG PENG CHO [US] ET AL) 11 August 1998 (1998-08-11) cited in the application the whole document	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2006	18/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, Claire

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/026521

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/026521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004037247 A	06-05-2004	AU 2003286604 A1	13-05-2004
US 5792783 A	11-08-1998	AT 200863 T	15-05-2001
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		US 5883113 A	16-03-1999