Title: NOVEL COMPOUNDS AND COMPOSITIONS AS PROTEIN KINASE INHIBITORS

Abstract: The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated tyrosine kinase activity, particularly diseases associated with the activity of PDGF-R, c-Kit and Bcr-abl.
NOVEL COMPOUNDS AND COMPOSIONS AS PROTEIN KINASE INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Application No. 60/460,838, filed April 4, 2003, which application is incorporated herein by reference for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated tyrosine kinase activity, particularly diseases associated with the activity of PDGF-R, c-Kit and Bcr-abl.

Background

[0003] The protein kinases represent a large family of proteins, which play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. These kinases include receptor tyrosine kinases, such as platelet-derived growth factor receptor kinase (PDGF-R), the receptor kinase for stem cell factor, c-Kit, and non-receptor tyrosine kinases, such as the fusion kinase Bcr-abl.

[0004] Chronic myeloid leukemia (CML) is an extensively studied human cancer that is caused by a reciprocal translocation that fuses the Abl proto-oncogene on chromosome 9 with a gene on chromosome 22 called Bcr. The resulting fusion protein Bcr-abl is capable of transforming B-cells by increasing mitogenic activity, reducing sensitivity to apoptosis and altering the adhesion and homing of CML progenitor cells. STI-571 (Gleevec) is an inhibitor of the oncogenic Bcr-abl tyrosine kinase and is used for the treatment of chronic myeloid leukemia (CML). However, some patients in the blast crisis stage of CML are resistant to STI-571 due to mutations in the Bcr-abl kinase.

[0005] The novel compounds of this invention inhibit one or more kinases; in particular wild type and one or more of the mutant forms of Bcr-abl and are, therefore, useful in the treatment of kinase-associated diseases, particularly Bcr-abl kinase associated diseases.
BRIEF SUMMARY OF THE INVENTION

[0006] In one aspect, the present invention provides compounds of Formula I:

\[
\begin{align*}
X^1 & \quad X^2 \\
R^1 & \quad R^3 \\
R^2 & \quad \text{L} \\
R^4 & \quad \text{and} \quad \text{L} \quad \text{is selected from the group consisting of} \quad -O- \quad \text{and} \quad -\text{NR}^5-,
\end{align*}
\]

wherein \( R^1 \) is hydrogen or \( C_{1-4}\)-alkyl;

[0007] \( X^1 \) and \( X^2 \) are independently selected from the group consisting of \(-N=\) and \(-\text{CR}^4=\), wherein \( R^4 \) is hydrogen or \( C_{1-4}\)-alkyl;

[0008] \( \text{L} \) is selected from the group consisting of a bond, \(-O-\) and \(-\text{NR}^5-\), wherein \( R^5 \) is hydrogen or \( C_{1-4}\)-alkyl;

[0009] \( R^1 \) is selected from the group consisting of \(-X^3\text{NR}^6\text{R}^7\), \(-X^3\text{OR}^7\) and \(-X^3\text{R}^7\), wherein \( X^3 \) is a bond or \( C_{1-4}\)-alkylene, \( R^6 \) is hydrogen or \( C_{1-4}\)-alkyl and \( R^7 \) is selected from the group consisting of \( C_{6-10}\)-aryl and \( C_{5-8}\)-heteroaryl; wherein any aryl or heteroaryl is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, amino, \( C_{1-4}\)-alkyl, halo-substituted \( C_{1-4}\)-alkyl, \( C_{1-4}\)-alkoxy and halo-substituted \( C_{1-4}\)-alkoxy;

[0010] \( R^2 \) is selected from the group consisting of hydrogen, halo, amino, \( C_{1-4}\)-alkyl, halo-substituted \( C_{1-4}\)-alkyl, \( C_{1-4}\)-alkoxy and halo-substituted \( C_{1-4}\)-alkoxy;

[0011] \( R^3 \) is selected from the group consisting of \( C_{3-8}\)-heterocycloalkyl-\( C_{6-10}\)-alkyl, \( C_{5-10}\)-heteroaryl-\( C_{6-10}\)-alkyl and \( C_{6-10}\)-aryl-\( C_{6-10}\)-alkyl; wherein any alkyl group is optionally substituted with 1 to 3 radicals selected from the group consisting of hydroxy, halo and amino; and any aryl, heteroaryl or heterocycloalkyl is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, nitro, \( C_{1-4}\)-alkyl, halo-substituted \( C_{1-4}\)-alkyl, hydroxy-\( C_{1-4}\)-alkyl, \( C_{1-4}\)-alkoxy, halo-substituted \( C_{1-4}\)-alkoxy, phenyl, \( C_{3-8}\)-heterocycloalkyl, \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)R}^9\), \(-X^3\text{S(O)NR}^8\text{R}^8\), \(-X^3\text{NR}^8\text{R}^9\), \(-X^3\text{NR}^8\text{R}^9\), \(-X^3\text{S(O)NR}^8\text{R}^8\), \(-X^3\text{S(O)R}^9\), \(-X^3\text{NR}^8\text{R}^9\), \(-X^3\text{NR}^8\text{R}^9\), \(-X^3\text{NR}^8\text{S(O)R}^9\), \(-X^3\text{NR}^8\text{S(O)R}^9\), \(-X^3\text{NR}^8\text{S(O)R}^9\), \(-X^3\text{NR}^8\text{S(O)R}^9\), \(-X^3\text{S(O)R}^9\), \(-X^3\text{S(O)R}^9\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), \(-X^3\text{C(O)NR}^8\text{R}^8\), wherein phenyl can be further substituted by
a radical selected from -NR²R⁸ or -C(O)NR²R⁸; X³ is as described above; R⁸ is hydrogen, C₆₋₁₀alkyl, hydroxy-C₆₋₁₀alkyl or C₂₋₆alkenyl; and R⁹ is hydroxy, C₆₋₁₀aryl-C₆₋₁₀alkyl, C₆₋₁₀aryl-C₆₋₁₀alkoxy, C₅₋₁₀heteroaryl-C₆₋₁₀alkyl, C₃₋₇heterocycloalkyl-C₆₋₁₀alkyl or C₃₋₇cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl of R⁹ is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, cyano, amino, nitro, C₆₋₁₀alkyl, hydroxy-C₆₋₁₀alkyl, halo-substituted C₆₋₁₀alkyl, C₆₋₁₀alkoxy, halo-substituted C₆₋₁₀alkoxy, halo-alkyl-substituted phenyl, benzoxyl, C₅₋₁₀heteroaryl, C₃₋₇heterocycloalkyl, -C(O)NR²R⁸, -S(O)₂NR²R⁸, -NR²R⁸, -C(O)R¹⁰ and -NR¹¹R¹¹, wherein R¹⁰ is C₅₋₁₀heteroaryl and R¹¹ is hydroxy-C₆₋₁₀alkyl;

[0012] and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g., hydrates) of such compounds.

[0013] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0014] In a third aspect, the present invention provides a method of treating a disease in an animal in which inhibition of kinase activity, particularly Bcr-abl activity, can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0015] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which kinase activity, particularly Bcr-abl activity, contributes to the pathology and/or symptomology of the disease.

[0016] In a fifth aspect, the present invention provides a method for inhibiting Bcr-abl activity, the method comprising contacting Bcr-abl with a compound that binds to a myristoyl binding pocket of Bcr-abl.

[0017] In a sixth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.
I. Definitions

[0018] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures for organic and analytical chemistry are those well known and commonly employed in the art.

[0019] “Alkyl” means a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. “Lower alkyl” has up to and including 7, preferably up to and including 4 carbons. For example, C₁₋₄alkyl includes methyl, ethyl, propyl, butyl, isopropyl or isobutyl. Alkenyl is as defined for alkyl with the inclusion of at least one double bond. For example, alkenyl includes vinyl, propenyl, isopropenyl, butenyl, isobutenyl or butadienyl. “Halo-substituted-alkyl” is alkyl as defined above where some or all of the hydrogen atoms are substituted with halogen atoms. For example, halo-substituted-alkyl includes trifluoromethyl, fluoromethyl, 1,2,3,4,5-pentafluoro-phenyl, etc. “Hydroxy-alkyl” includes, for example, hydroxymethyl, hydroxymethyl, etc.

[0020] “Alkoxy” is as defined for alkyl with the inclusion of an oxygen atom, for example, methoxy, ethoxy, etc. “Halo-substituted-alkoxy” is as defined for alkoxy where some or all of the hydrogen atoms are substituted with halogen atoms. For example, halo-substituted-alkoxy includes trifluoromethoxy, etc.

[0021] “Aryl” means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl may be phenyl or naphthyl, preferably phenyl. “Arylene” means a divalent radical derived from an aryl group. “Heteroaryl” is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzo[1,3]dioxole, imidazolyl, benzo- imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thiienyl, etc.

[0022] “Cycloalkyl” means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C₃₋₁₀cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. “Heterocycloalkyl” means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - or -S(O)₂-, wherein R is hydrogen, C₁₋₄alkyl or a
nitrogen protecting group. For example, C₃₋₈-heterocycloalkyl-C₀₋₄-alkyl as used in this application to describe compounds of the invention includes morpholino, morpholino-methyl, morpholino-ethyl, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylole, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

[0023] "Halogen" (or halo) preferably represents chloro or fluoro, but may also be bromo or iodo.

[0024] Pharmaceutically acceptable salts of the acidic compounds of the present invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

[0025] Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids, e.g., hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

[0026] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

[0027] "Inhibition", "inhibits" and "inhibitor" refer to a compound that prohibits or a method of prohibiting, a specific action or function.

[0028] "Therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

[0029] "Composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and deleterious to the recipient thereof.

[0030] "Subject" refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In certain embodiments, the subject is a human.

[0031] "IC₅₀" is the concentration of a compound that results in 50% inhibition of activity of a peptide, protein, enzyme or biological process.
“Myristoyl Binding Pocket” is a region of Bcr-abl at which a myristoyl moiety can bind when the BCR-Abl protein is in an appropriate conformation for myristoyl binding. Myristoyl binding pockets are described in, for example, Hantschel et al., “A Myristoyl/Phosphotyrosine Switch Regulates c-Abl” Cell (2003), Vol. 112, 845-857 and Bhushan et al., “Structural Basis for the Autoinhibition of c-Abl Tyrosine Kinase” Cell (2003), Vol. 112, 859-871.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

II. General

The fusion protein Bcr-Abl is a result of a reciprocal translocation that fuses the Abl proto-oncogene with the Bcr gene. Bcr-abl is then capable of transforming B-cells through the increase of mitogenic activity. This increase results in a reduction of
sensitivity to apoptosis, as well as altering the adhesion and homing of CML progenitor cells. The present invention provides compounds, compositions and methods for the treatment of kinase related disease, particularly PDGF-R, c-Kit and Bcr-abl kinase related diseases. For example, leukemia and other proliferation disorders related to Bcr-abl, can be treated through the inhibition of wild-type and mutant forms of Bcr-abl.

III. Compounds

A. Preferred Compounds

[0038] In some embodiments, with reference to compounds of Formula Ia, compounds of the invention can be of Formula Ia:

\[
\text{(Ia)}
\]

in which \( L \) is a bond; \( R^1 \) is selected from the group consisting of \(-\text{NHR}^7\), \(-\text{OR}^7\) and \(-\text{R}^7\), wherein \( R^7 \) is phenyl or pyridinyl, optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, amino, \( C_{1-4}\text{alkyl} \), halo-substituted \( C_{1-4}\text{alkyl} \), \( C_{1-4}\text{alkoxy} \) and halo-substituted \( C_{1-4}\text{alkoxy} \); and \( R^2 \) is hydrogen or \( C_{1-4}\text{alkyl} \).

[0039] In a further embodiment, \( R^2 \) is \( C_{6-10}\text{aryl}-C_{0-4}\text{alkyl} \), optionally substituted with 1 to 3 radicals independently selected from the group consisting of \(-\text{C(O)NR}^8\text{R}^8\), \(-\text{C(O)NR}^8\text{R}^9\), \(-\text{C(O)R}^9\) and \(-\text{C(O)NR}^8\text{(CH}_2\text{)}_2\text{NR}^8\text{R}^8\), wherein \( R^8 \) is hydrogen, \( C_{1-6}\text{alkyl} \) or hydroxy-\( C_{1-6}\text{alkyl} \); and \( R^9 \) is \( C_{3-8}\text{heterocycloalkyl}-C_{0-4}\text{alkyl} \), optionally substituted by \(-\text{C(O)NR}^8\text{R}^8\).

[0040] In yet a further embodiment, \( R^1 \) is \(-\text{NHR}^7\), wherein \( R^7 \) is phenyl substituted with halo-substituted \( C_{1-4}\text{alkyl} \) or halo-substituted \( C_{1-4}\text{alkoxy} \); \( R^2 \) is hydrogen; and \( R^3 \) is phenyl substituted with \(-\text{C(O)NH(CH}_2\text{)}_2\text{OH}, -\text{C(O)NHR}^9\), \(-\text{C(O)R}^9\) or \(-\text{NH(CH}_2\text{)}_2\text{N(CH}_3\text{)}_2\), wherein \( R^9 \) is morpholino-ethyl or piperidinyl, substituted with \(-\text{C(O)NH}_2\).

[0041] In another embodiment, compounds of the invention can be of Formula Ib:
in which L is a bond; R$^1$ is selected from the group consisting of -NHR$^7$, -OR$^7$ and -R$^7$, wherein R$^7$ is phenyl or pyridinyl optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, amino, C$_{1,4}$alkyl, halo-substituted C$_{1,4}$alkyl, C$_{1,4}$alkoxy and halo-substituted C$_{1,4}$alkoxy; and R$^2$ is hydrogen or C$_{1,4}$alkyl.

[0042] In a further embodiment, R$^3$ is selected from C$_{5,6}$heteroaryl-C$_{0,4}$alkyl or C$_{6,10}$aryl-C$_{0,4}$alkyl; wherein any aryl or heteroaryl is optionally substituted with 1 to 3 radicals selected from the group consisting of C$_{3,8}$heterocycloalkyl, -C(O)NR$^8$R$^8$, -C(O)NR$^8$R$^9$, -C(O)R$^9$, -NR$^8$R$^9$ and -NR$^8$(CH$_2$)$_n$NR$^8$R$^8$, wherein R$^8$ is hydrogen, C$_{1,4}$alkyl or hydroxy-C$_{1,4}$alkyl; and R$^3$ is C$_{6,10}$aryl-C$_{0,4}$alkyl, C$_{5,10}$heteroaryl-C$_{0,4}$alkyl, C$_{3,8}$heterocycloalkyl-C$_{0,4}$alkyl or C$_{3,8}$cycloalkyl; wherein any aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl of R$^3$ is further optionally substituted by up to 2 radicals selected from the group consisting of hydroxy, C$_{1,4}$alkyl, hydroxy-C$_{1,4}$alkyl, C$_{3,8}$heterocycloalkyl, -C(O)NR$^8$R$^8$ and -S(O)$_2$NR$^8$R$^8$.

[0043] In yet a further embodiment, R$^1$ is -NHR$^7$, wherein R$^7$ is phenyl substituted with halo-substituted C$_{1,4}$alkyl or halo-substituted C$_{1,4}$alkoxy; R$^2$ is hydrogen; and R$^3$ is pyridinyl or phenyl, optionally substituted with 1 to 3 radicals selected from the group consisting of -C(O)NH(CH$_2$)$_2$OH, -C(O)NHCH(C$_3$H$_7$)$_2$CH$_2$OH, -C(O)NH(CH$_2$)$_2$CH$_3$, -C(O)N(CH$_3$)$_2$, -C(O)NH(CH$_2$)$_2$N(CH$_3$)$_2$, -C(O)NHR$^9$, -C(O)N(C$_2$H$_5$)$_2$R$^9$ and -C(O)R$^9$, wherein R$^9$ is phenyl, phenethyl, pyridinyl, pyrrolidinyl, piperidinyl, morpholino or morpholino-ethyl; wherein any aryl, heteroaryl, heterocycloalkyl or alkyl of R$^3$ is further optionally substituted by up to 2 radicals selected from the group consisting of hydroxy, C$_{1,4}$alkyl, -CH$_2$OH, -(CH$_2$)$_2$OH, pyrrolidinyl, piperazinyl, -C(O)NH$_2$, -C(O)N(C$_2$H$_5$)$_2$ and -S(O)$_2$NH$_2$.

[0044] In another embodiment, compounds of the invention can be of Formula Ic:
in which L is a bond, -NH-, -N(C\textsubscript{2}H\textsubscript{5})- or -O-; R\textsuperscript{1} is selected from the group consisting of -NHR\textsuperscript{7}, -OR\textsuperscript{7} and -R\textsuperscript{7}, wherein R\textsuperscript{7} is phenyl or pyridinyl, optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, amino, C\textsubscript{1-4}alkyl, halo-substituted C\textsubscript{1-4}alkyl, C\textsubscript{1-4}alkoxy and halo-substituted C\textsubscript{1-4}alkoxy; and R\textsuperscript{2} is hydrogen or C\textsubscript{1-4}alkyl.

[0045] In a further embodiment, L is a bond; and R\textsuperscript{3} is selected from the group consisting of C\textsubscript{3-8}heterocycloalkyl-C\textsubscript{0-4}alkyl, C\textsubscript{5-10}heteroaryl-C\textsubscript{0-4}alkyl and C\textsubscript{6-10}aryl-C\textsubscript{0-4}alkyl; wherein any aryl, heteroaryl or heterocycloalkyl is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, nitro, C\textsubscript{1-4}alkyl, hydroxy-C\textsubscript{1-4}alkyl, C\textsubscript{1-4}alkoxy, C\textsubscript{3-8}heterocycloalkyl, -X\textsuperscript{3}C(O)NR\textsuperscript{8}R\textsuperscript{8}, -X\textsuperscript{3}C(O)NR\textsuperscript{6}R\textsuperscript{9}, -X\textsuperscript{3}NR\textsuperscript{8}R\textsuperscript{8}, -X\textsuperscript{3}NR\textsuperscript{6}R\textsuperscript{9}, -X\textsuperscript{3}S(O)NR\textsuperscript{8}R\textsuperscript{8}, -X\textsuperscript{3}S(O)NR\textsuperscript{6}R\textsuperscript{9}, -X\textsuperscript{3}S(O)\textsuperscript{2}R\textsuperscript{8}, -X\textsuperscript{3}S(O)\textsuperscript{2}R\textsuperscript{9}, -X\textsuperscript{3}S(C)\textsuperscript{2}R\textsuperscript{8}, -X\textsuperscript{3}S(C)\textsuperscript{2}R\textsuperscript{9}, -X\textsuperscript{3}NR\textsuperscript{8}S(O)\textsuperscript{2}R\textsuperscript{8}, -X\textsuperscript{3}NR\textsuperscript{8}S(O)\textsuperscript{2}R\textsuperscript{9}, -X\textsuperscript{3}NR\textsuperscript{6}S(O)\textsuperscript{2}R\textsuperscript{8}, -X\textsuperscript{3}NR\textsuperscript{6}S(O)\textsuperscript{2}R\textsuperscript{9}, -X\textsuperscript{3}NR\textsuperscript{8}C(O)NR\textsuperscript{8}R\textsuperscript{8}, -X\textsuperscript{3}NR\textsuperscript{8}C(O)NR\textsuperscript{6}R\textsuperscript{9}, -X\textsuperscript{3}NR\textsuperscript{6}C(O)NR\textsuperscript{8}R\textsuperscript{8}, -X\textsuperscript{3}NR\textsuperscript{6}C(O)NR\textsuperscript{6}R\textsuperscript{9} and

- X\textsuperscript{3}O(CH\textsubscript{2})\textsubscript{1-4}NR\textsuperscript{8}R\textsuperscript{8}, R\textsuperscript{8} is hydrogen, C\textsubscript{1-6}alkyl or hydroxy-C\textsubscript{1-6}alkyl; R\textsuperscript{9} is C\textsubscript{6-10}aryl-C\textsubscript{0-4}alkyl, C\textsubscript{6-10}aryloxy, C\textsubscript{5-10}heteroaryl-C\textsubscript{0-4}alkyl, C\textsubscript{3-8}heterocycloalkyl-C\textsubscript{0-4}alkyl or C\textsubscript{3-8}cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl of R\textsuperscript{9} is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, cyano, nitro, C\textsubscript{1-4}alkyl, hydroxy-C\textsubscript{1-4}alkyl, halo-substituted C\textsubscript{1-4}alkyl, C\textsubscript{1-4}alkoxy, halo-alkyl-substituted-phenyl, benzoxy, C\textsubscript{5-10}heteroaryl, C\textsubscript{3-8}heterocycloalkyl, -C(O)NR\textsuperscript{8}R\textsuperscript{8}, -S(O)\textsubscript{2}NR\textsuperscript{8}R\textsuperscript{8}, -NR\textsuperscript{8}R\textsuperscript{8} and -C(O)R\textsuperscript{10}, wherein R\textsuperscript{10} is C\textsubscript{5-8}heteroaryl.

[0046] In a further embodiment, R\textsuperscript{3} is selected from the group consisting of morpholino, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, 4-oxo-piperdin-1-yl, piperazinyl, pyrrolidinyl, pyridinyl, phenyl, naphthyl, thiophenyl, benzofuran-2-yl, benzo[1,3]dioxolyl, piperidinyl, pyrazinyl, pyrimidinyl, imidazolyl, pyrazolyl and 1H-benzoimidazolyl; wherein any aryl, heteroaryl or heterocycloalkyl is optionally substituted with 1 to 2 radicals independently selected from the group consisting of chloro, methyl, ethyl, hydroxymethyl, methoxy, -C(O)OH, -C(O)H, -C(O)OCH\textsubscript{3}, -C(O)N(C\textsubscript{2}H\textsubscript{5})\textsubscript{2}, -C(O)N(CH\textsubscript{3})\textsubscript{2}, -C(O)NHCH\textsubscript{3}, -S(O)\textsubscript{2}NH\textsubscript{2}, -S(O)\textsubscript{2}CH\textsubscript{3}, chloro, -NH\textsubscript{2}, -C(O)CH\textsubscript{3}, =NOCH\textsubscript{3}, -NH(CH\textsubscript{2})\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2},

-NH(CH\textsubscript{2})\textsubscript{3}NH\textsubscript{2}, -NH(CH\textsubscript{2})\textsubscript{2}OH, -C(O)NH(CH\textsubscript{2})\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2}, -NHR\textsuperscript{9}, -O(CH\textsubscript{2})\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2},
morpholino, piperazinyl, -NHC(O)CH₃, -NHC(O)NHC₄H₉, -C(O)NHC₄H₉, -C(O)NHC₃H₇, -C(O)NHC₅H₁₈OH, -C(O)N(C₂H₄OH)₂, -C(O)NHC₃H₄OH, -C(O)NH(CH₂)₂OH, -NHC(O)R⁹, -C(O)NHR⁹, -NHC(O)NHR⁹, -C(O)R⁹, -NHS(O)₂C₄H₉, -NHS(O)₂CH₃, -NHS(O)₃R⁹, -S(O)₂R⁹, -S(O)₂NHR⁹, -C(O)NH₂ and -C(O)NH(CH₂)₂N(CH₃)₂; R⁹ is phenethyl, 2-phenoxy-ethyl, 1H-imidazolyl-propyl, pyrindinyl, pyridinyl-methyl, quinolinyl, morpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydro-furan-2-ylmethyl, furan-2-ylmethyl, thiazol-2-ylmethyl, benzo[1,3]dioxol-5-ylmethyl, benzo[1,3]dioxol-5-yl, 3-(2-oxo-pyrrolidin-1-yl)-propyl, 3-imidazol-1-yl-propyl, 3H-pyrazol-3-yl, morpholino-ethyl, phenyl, thiophenyl-methyl, benzyl, cyclohexyl or furan-2-ylmethyl; wherein said aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl of R⁹ is further optionally substituted by up to 2 radicals selected from hydroxy-methyl, hydroxy-ethyl, isobutyl, nitro, amino, hydroxyl, methoxy, trifluoromethoxy, cyano, isopropyl, methyl, ethyl, chloro, fluoro, pyrindinyl, morpholino, phenoxy, pyrrolidinyl, trifluoromethyl, trifluoromethyl-substituted-phenyl, -N(CH₃)₂, -C(O)NH₂, -S(O)₂NH₂, -C(O)N(CH₃)₂, cyano or -C(O)R¹⁰, and R¹⁰ is furanyl.

[0047] In a further embodiment, L is -NH-, -N(C₂H₅)- or -O-; and R³ is selected from the group consisting of C₅-₁₀heteroaryl-C₆-alkyl and C₆-₁₀aryl-C₆-alkyl; wherein any aryl or heteroaryl is optionally substituted with 1 to 3 radicals independently selected from the group consisting of C₁-₄alkoxy, C₃-₈heterocycloalkyl, -X³C(O)NR⁸R⁸, -X³S(O)₂NR⁸R⁸, -X³NR⁸C(O)R⁸ and -X³NR⁸C(O)NR⁸R⁸; R⁸ is hydrogen or C₁-₄alkyl; and R⁹ is C₆-₁₀aryl-C₆-alkyl optionally substituted by up to 2 halo-substituted C₁-₄alkyl radicals.

[0048] In yet a further embodiment, R³ is selected from the group consisting of quinolinyl, pyridinyl and phenyl; wherein any aryl or heteroaryl is optionally substituted with 1 to 2 radicals independently selected from the group consisting of morpholino, methoxy, -C(O)NH₂, -NHC(O)NHR⁹ and -S(O)₂NH₂; and R⁹ is phenyl substituted by trifluoromethyl.

[0049] Preferred compounds of Formula I are detailed in the Examples and Table I, infra.

B. Preparation of Compounds

[0050] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice,

[0051] Compounds of Formula I, wherein L is a bond, can be prepared by proceeding as in the following Reaction Scheme 1:

\[
\begin{align*}
\text{Reaction Scheme 1} \\
\text{Q} \\
\text{R}^1 \quad \text{X}^1 \quad \text{X}^2 \\
\text{R}^2 \\
\text{(2)} \\
\text{R}^3 \text{–} \text{B(OH)}_2 \\
\text{(3)} \\
\text{R}^3 \\
\text{R}^1 \quad \text{X}^1 \quad \text{X}^2 \\
\text{R}^2 \\
\text{I}
\end{align*}
\]

in which \(X^1, X^2, R^1, R^2,\) and \(R^3\) are as defined for Formula I above and Q represents a halo group, for example iodo or chloro, preferably chloro.

[0052] Compounds of Formula I can be prepared by reacting a compound of Formula 2 with a compound of Formula 3. The reaction can be effected in the presence of a suitable catalyst (e.g., Pd(PPh₃)₄, etc.), in an appropriate solvent (e.g., acetonitrile) and with an appropriate base (e.g., Na₂CO₃) at 50-100°C and requires 5-15 hours to complete.

[0053] Compounds of Formula I, wherein L is a bond, can also be prepared by proceeding as in the following Reaction Scheme 2:
in which $X^1$, $X^2$, $R^1$, $R^2$ and $R^3$ are as defined for Formula I above and $Q$ represents a halo group, for example iodo or chloro, preferably iodo.

[0054] Compounds of Formula I can be prepared by reacting a compound of Formula 2 with a compound of Formula 4. The reaction can be effected in the presence of a suitable catalyst (e.g., Pd(PPh$_3$)$_4$, etc.) and in an appropriate solvent (e.g., 1,4-dioxane) at 60-110°C and requires 10-20 hours to complete.

[0055] Compounds of Formula I, wherein $L$ is $-O-$, can be prepared by proceeding as in the following Reaction Scheme 3:
in which X₁, X₂, R¹, R² and R³ are as defined for Formula I above and Q represents a halo group, for example iodo or chloro, preferably chloro.

[0056] Compounds of Formula I can be prepared by reacting a compound of Formula 2 with a compound of Formula 5. The reaction can be effected in the presence of a suitable base (e.g., KO'Bu, etc.) and in an appropriate solvent (e.g., THF) at 50-100°C and requires 5-10 hours to complete.

[0057] Compounds of Formula I, wherein L is --NR₅--, can be prepared by proceeding as in the following Reaction Scheme 4:
in which $X^1$, $X^2$, $R^1$, $R^2$, $R^3$ and $R^5$ are as defined for Formula I above and $Q$ represents a halo group, for example iodo or chloro, preferably chloro.

[0058] Compounds of Formula I can be prepared by reacting a compound of Formula 2 with a compound of Formula 6. The reaction can be effected in the presence of a suitable ligand (e.g., IprHCl, etc.), a suitable catalyst (e.g., Pd$_2$(dba)$_3$, etc.), a suitable base (e.g., KO'Bu, etc.) and in an appropriate solvent (e.g., 1,4-dioxane, THF, etc.) at 50-100°C and requires 2-10 hours to complete.

[0059] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0060] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition
salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.)

**[0061]** Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

**[0062]** Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamyating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, paranitrophenyl carbonate, or the like).

**[0063]** Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, “Protecting Groups in Organic Chemistry”, 3rd edition, John Wiley and Sons, Inc., 1999.

**[0064]** Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

**[0065]** Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in
racemization. A more detailed description of the techniques applicable to the resolution of
diestereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre
Collet, Samuel H. Wilen, “Enantiomers, Racemates and Resolutions”, John Wiley And Sons,

[0066] In summary, the compounds of Formula I can be made by a process,
which involves:

(a) reacting a compound of Formula 2 with a compound of Formula 3, 4, 5 or
6:

\[
\begin{array}{cccc}
X^1 & X^2 & R^1 & R^2 \\
(2) & & & \\
& R^3 & R^3 & R^3 & R^3 & R^3 \\
& B(OH)_2 & -SnBu_3 & -OH & -NR^5H \\
(3) & (4) & (5) & (6)
\end{array}
\]

in which \(X^1, X^2, R^1, R^2, R^3\) and \(R^5\) are as defined for Formula I above and \(Q\) represents a
fluoro, chloro, bromo or iodo; or

(b) optionally converting a compound of the invention into a
pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-
salt form;

(d) optionally converting an unoxidized form of a compound of the invention
into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to
its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention
from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a
pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention
to its non-derivatized form.

[0067] Insofar as the production of the starting materials is not particularly
described, the compounds are known or can be prepared analogously to methods known in
the art or as disclosed in the Examples hereinafter.
[0068] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

IV. Compositions

[0069] The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal, topical, and parenteral administration to mammals, including man, to inhibit Bcr-abl activity, and for the treatment of Bcr-abl dependent disorders, in particular cancer and tumor diseases, such as leukemias (especially chronic myeloid leukemia and acute lymphoblastic leukemia), and comprise an effective amount of a pharmacologically active compound of the present invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

[0070] More particularly, the pharmaceutical compositions comprise an effective Bcr-abl inhibiting amount of a compound of the present invention.

[0071] The pharmacologically active compounds of the present invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or mixture with excipients or carriers suitable for either enteral or parenteral application.

[0072] Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethylene glycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are preferably prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.
[0073] Tablets may be either film coated or enteric coated according to methods known in the art.

[0074] Suitable formulations for transdermal application include an effective amount of a compound of the present invention with carrier. Preferred carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations may also be used.

[0075] Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0076] The pharmaceutical formulations contain an effective Bcr-abl inhibiting amount of a compound of the present invention as defined above, either alone or in combination with another therapeutic agent.

[0077] In conjunction with another active ingredient, a compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

[0078] The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg of the active ingredient.

V. Methods

[0079] The compounds of Formula I in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the in vitro tests described within “Assays”, infra, and are therefore indicated for therapy of diseases and disorders associated with Bcr-abl activity. For Bcr-abl, compounds of Formula I preferably show an IC_{50} in the range of 1 x 10^{-10} to 1 x 10^{-5} M, preferably less than 1μM for wild-type Bcr-abl and at least two other Bcr-abl mutants (mutants selected from G250E, E255V, T315I, F317L and M351T). For example, compound 97 (Table I) has an
IC\textsubscript{50} of 0.20, 4.78, 0.25, 5.28, 4.45, and 0.97 for wild-type, G250E, E255V, T315I, F317L and M351T Bcr-abl, respectively.

[0080] The invention also provides a method for preventing or treating diseases or conditions comprising abnormal cell growth in a mammal, including a human, comprising administering to the mammal a compound of Formula I in an amount effective to inhibit PDGF-R, c-Kit and/or Bcr-abl activity.

[0081] PDGF (Platelet-derived Growth Factor) is a very commonly occurring growth factor, which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis.

[0082] Compounds of Formula I can inhibit PDGF-R and are, therefore, also suitable for the treatment of tumor diseases, such as gliomas, sarcomas, prostate tumors, and tumors of the colon, breast, and ovary.

[0083] The compounds of the present invention also inhibit cellular processes involving stem-cell factor (SCF, also known as the c-kit ligand or steel factor), such as SCF receptor (kit) autophosphorylation and the SCF-stimulated activation of MAPK kinase (mitogen-activated protein kinase).

[0084] The compounds of the present invention, thus inhibit also the autophosphorylation of SCF receptor (and c-kit, a proto-oncogen). MO7e cells are a human promegakaryocytic leukemia cell line, which depends on SCF for proliferation. A compound of Formula I, inhibits the autophosphorylation of SCF-R in the micromolar range.

[0085] On the basis of the described properties, the compounds of the present invention, can be used not only as a tumor-inhibiting substance, for example in small cell lung cancer, but also as an agent to treat non-malignant proliferative disorders, such as atherosclerosis, thrombosis, psoriasis, scleroderma, and fibrosis, as well as for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluorouracil, and in asthma. It can especially be used for the treatment of diseases, which respond to an inhibition of the PDGF-R kinase.

[0086] In addition, the compounds of the present invention can be used in combination with other anti-tumor agents.

[0087] Also abl kinase, especially v-abl kinase, is inhibited by compounds of the present invention. By analogy, the compounds of the present invention also inhibit Bcr-abl kinase and are thus suitable for the treatment of Bcr-abl-positive cancer and tumor diseases, such as leukemias (especially chronic myeloid leukemia and acute lymphoblastic
leukemia, where especially apoptotic mechanisms of action are found), and also shows
effects on the subgroup of leukemic stem cells as well as potential for the purification of
these cells in vitro after removal of said cells (for example, bone marrow removal) and
reimplantation of the cells once they have been cleared of cancer cells (for example,
reimplantation of purified bone marrow cells).

[0083] In addition, the compounds of the present invention show useful
effects in the treatment of disorders arising as a result of transplantation, for example,
allogenic transplantation, especially tissue rejection, such as especially obliterative
bronchiolitis (OB), i.e. a chronic rejection of allogenic lung transplants. In contrast to
patients without OB, those with OB often show an elevated PDGF concentration in
bronchoalveolar lavage fluids. Synergistic effects with other immunomodulatory or anti-
inflammatory substances are possible, for example when used in combination with
cyclosporin, rapamycin, or ascomycin, or immunosuppressant analogues thereof, for example
cyclosporin A (CsA), cyclosporin G, FK-506, rapamycin, or comparable compounds,
corticosteroids, cyclophosphamide, azathioprine, methotrexate, brequinar, leflunomide,
mizoribine, mycophenolic acid, mycophenolate mofetil, 15-deoxyspergualin,
immunosuppressant antibodies, especially monoclonal antibodies for leukocyte receptors, for
example MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands, or
other immunomodulatory compounds, such as CTLA4Ig.

[0089] The compounds of the present invention are also effective in diseases
associated with vascular smooth-muscle cell migration and proliferation (where PDGF and
PDGF-R often also play a role), such as restenosis and atherosclerosis. These effects and the
consequences thereof for the proliferation or migration of vascular smooth-muscle cells in
vitro and in vivo can be demonstrated by administration of the compounds of the present
invention, and also by investigating its effect on the thickening of the vascular intima
following mechanical injury in vivo.

[0090] Furthermore, the present invention provides a method for inhibiting
Bcr-abl activity, the method comprising contacting Bcr-abl with a compound that binds to a
myristoyl binding pocket of Bcr-abl. In a preferred embodiment, the compound is a
compound of Formula I.
VI. Examples

A. Compounds

[0091] The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula I (Examples), and their intermediates (References), according to the invention.

[0092] Reference 1. (6-Chloro-pyrimidin-4-yl)-(4-trifluoromethoxy-phenyl)-amine

![Chemical Structure]

[0093] 1.0 g 4,6-dichloropyrimidine (6.7mmol) is dissolved with 1.2g p-trifluoromethoxy aniline (6.7 mmol) in 15 mL ethanol, then 1.75 mL DIEA (10 mmol) is added. Reaction is under reflux for 2 hours, and cooled down to room temperature. After evaporating the solvent, the crude product is purified by flash chromatography (EA/Hexane=3:7) to give (6-Chloro-pyrimidin-4-yl)-(4-trifluoromethoxy-phenyl)-amine as a white solid 1.94 g.

[0094] Reference 2. 4-[6-(4-Trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzoic acid

![Chemical Structure]

[0095] 200 mg (4-Chloro-pyrimidin-6-yl)-(4-trifluoromethoxy-phenyl)-amine (0.69 mmol), prepared as in Reference 1, is added to a flask with 115 mg 4-carboxyphenylboronic acid (0.69 mmol), 40 mg palladium tetrakis triphenylphosphine (0.034 mmol) and 292 mg of sodium carbonate (2.76 mmol). Solvent MeCN/H2O (1:1) 10 mL is added into the flask. After refill with argon, the flask is heated to 90°C for 8 hours. The hot reaction solution is filtered and collected. 6N HCl solution is added to the solution until the pH is less than 5. The pale solid 4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzoic acid (220mg) is collected by filtration and rinsed by 5 mL water twice.

[0096] Reference 3. 4-[4-(4-Trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzoic acid
[0097] To 100 ml round bottom flask, 1.5 g of 2,4-Dichloro-[1,3,5]triazine (10 mmol), 231 mg of palladium tetrakis triphenylphosphine (0.2 mmol) and 20 ml of 0.5M 4-(ethoxy(carbonyl))-phenyl zinc iodide are mixed. 10 ml of dry THF is added to the reaction mixture. The reaction is carried out at room temperature, overnight. The product is used in the next step without further purification. p-Trifluoromethoxy-aniline (1.77 g; 10 mmol) is added and allowed to react at room temperature for 2 hours. After removal of THF by evaporation, the crude product is redissolved in ethyl acetate (100 ml) and washed with saturated ammonium chloride solution (100 ml; 3 times) and brine (once). The crude product is purified by a silica gel flash column to give 2.8 g of final product as a white solid.

[0098] 2.8 g 4-[4-(4-Trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzoic acid ethyl ester is dissolved in 50 ml of a water/acetonitrile (1:1) mixture. A solution of 19N NaOH (0.74 ml) is added and the reaction is refluxed at 80°C for 2 hours. The reaction is cooled to room temperature and the pH is adjusted to 5 by the addition of 6N HCl. The light yellow precipitate is collected, washed with 10 ml water and dried to give 4-[4-(4-trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzoic acid (2.4 g). MS: m/z 377.1 (M+H)+; 1H NMR (400 MHz, DMSO) δ 10.62 (s, 1H), 8.92 (s, 1H), 8.51 (d, J = 8.0 Hz, 2H), 8.14 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H), 7.54 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H).

[0099] Example 1. N,N-Dimethyl-4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzamide

[0100] 100 mg 4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzoic acid (0.27 mmol), prepared as in Reference 2, is added to 200 μL dimethylamine (2.0 M in THF, 0.40 mmol), HATU (112 mg; 0.30 mmol) and DIEA (232 μL; 1.33 mmol). After adding 4 mL solvent DMF, the reaction is stirred at room temperature for 8 hours. The
solvent is removed and the crude product is purified by flash chromatography using MeOH/DCM (5%/95%) resulting in N,N-dimethyl-4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzamide as a pale yellow solid (101 mg). MS: m/z 402.1 (M+H)+; 1H NMR (400MHz, DMSO) δ 8.80 (s, 1H), 8.05 (d, J=8.1Hz, 2H), 7.83 (d, J=9.1Hz, 2H), 7.58 (d, J=8.4Hz, 2H), 7.37 (d, J=8.4Hz, 2H), 7.30 (s, 1H), 2.97 (s, 6H).

Example 2. N-(2-Morpholin-4-yl-ethyl)-4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzamide

100 mg 4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzoic acid (0.27 mmol), prepared as in Reference 2, is added to 4-(2-aminoethyl)morpholine (53 µL; 0.40 mmol), HATU (112 mg; 0.30 mmol) and DIEA (232 µL; 1.33 mmol). DMF (4 mL) is added and the reaction stirred at room temperature for 8 hours. The solvent is removed and the crude product is purified by flash chromatography using MeOH/DCM (5%/95%) resulting in N-(2-morpholin-4-yl-ethyl)-4-[6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzamide as a pale yellow solid (123 mg). MS: m/z 488.1 (M+H)+; 1H NMR (400MHz, DMSO) δ 8.78 (s, 1H), 8.16 (d, J=8.3Hz, 2H), 8.03 (d, J=8.5Hz, 2H), 7.85 (d, J=10.2Hz, 2H), 7.36 (d, J=8.8Hz, 2H), 7.34 (s, 1H), 4.01 (t, 7.0Hz, 2H), 3.66 (t, 6.8Hz, 4H), 3.57 (t, 7.2Hz, 2H), 3.35 (t, 6.9Hz, 4H).

Example 3. (6-Pyridin-4-yl-pyrimidin-4-yl)-(4-trifluoromethoxy-phenyl)-amine

(4-Chloro-pyrimidin-6-yl)-(4-trifluoromethoxy-phenyl)-amine (100 mg; 0.35 mmol), prepared as in Reference 1, is added to 4-(tributyltin)-pyridine (190 mg; 0.52 mmol) and palladium tetrakis triphenylphosphine (20 mg; 0.018 mmol). Solvent is dry 1,4-dioxane. The reaction is carried out at reflux temperatures, under argon gas, for 16 hours. After removing the solvent, the crude product is purified by flash chromatography using
Hexane/EA (35%;65%) resulting in (6-Pyridin-4-yl-pyrimidin-4-yl)-(4-trifluoromethoxyphenyl)-amine as a yellow solid (40mg). MS: m/z 333.2 (M+H)^+; ^1H NMR (400MHz, CDCl₃) δ 8.83 (s, 1H), 8.79 (d, J=8.2Hz, 2H), 7.82 (d, J=9.0Hz, 2H), 7.51 (d, J=8.4Hz, 2H), 7.29 (d, J=8.4Hz, 2H), 7.09 (s, 1H).

Example 4. [6-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)-pyrimidin-4-yl]-
(4-trifluoromethoxy-phenyl)-amine

(4-Chloro-pyrimidin-6-yl)-(4-trifluoromethoxy-phenyl)-amine (100 mg; 0.35 mmol), prepared as in Reference 1, is added to 1,4-dioxo-8-aza-spiro-[4.5]-decane (75 mg; 0.52 mmol), tris-(dibenzylidene-acetone)-dipalladium (0) (8.1 mg; 0.009 mmol), 1,3-bis(2,6-di-I-propylphenyl)-imidazolium chloride 7.4 mg (0.018 mmol) and potassium tert-butoxide (59 mg; 0.52 mmol). Solvent is dry 1,4-dioxane. The reaction is carried out at 80°C for 4 hours under argon gas. After removing the solvent, the crude product is purified by flash chromatography using Hexane/EA (40%/60%) resulting in [6-(1,4-dioxo-8-aza-
spiro[4.5]dec-8-yl)-pyrimidin-4-yl]-
(4-trifluoromethoxy-phenyl)-amine as a white solid (110mg). MS: m/z 397.2 (M+H)^+; ^1H NMR (400MHz, CDCl₃) δ 8.27 (s, 1H), 7.33 (d, J=8.2Hz, 2H), 7.18 (d, J=8.4Hz, 2H), 6.66 (s, 1H), 3.99 (t, J=4.8Hz, 4H), 3.67 (t, J=5.2Hz, 4H), 1.70 (t, J=5.5Hz, 4H).

Example 5. [6-(3-Methanesulfonyl-phenyl)-pyrimidin-4-yl]-
(4-trifluoromethoxy-phenyl)-amine

To a degassed solution of (6-chloropyrimidin-4-yl)-(4-trifluoromethoxyphenyl)-amine (510 mg, 1.76 mmol), prepared as in Reference 1, and (3-methylsulfonylphenyl)-boronic acid (352 mg, 1.76 mmol) in 0.4 M sodium carbonate aqueous solution (17 mL) and acetonitrile (17 mL) is added PPh₃ (100 mg, 0.09 mmol). After stirring at about 90°C under N₂ for 12 hours, the reaction mixture is partitioned between
saturated NaHCO₃ and CHCl₃. The aqueous layer is extracted with additional CHCl₃. The combined organic layers are dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant yellowish oil is purified by column chromatography (SiO₂, hexane/ethyl acetate (4/6)) to give [6-(3-methanesulfonylphenyl)-pyrimidin-4-yl]-
(4-trifluoromethoxyphenyl)-amine as a pale yellowish solid (619 mg; 86%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.55-8.54 (m, 1H), 8.30-8.28 (m, 1H), 8.10-8.03 (m, 1H), 7.71-7.68 (m, 1H), 7.55-7.53 (m, 2H), 7.28-7.27 (m, 1H), 7.10-7.09 (m, 2H), 3.11 (s, 3H).

[0109] Example 6. 3-[6-(4-Trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzamide

![Chemical Structure](image)

[0110] To a degassed solution of (6-chloropyrimidin-4-yl)-
(4-trifluoromethoxyphenyl)-amine (73 mg, 0.25 mmol), prepared as in Reference 1, and
(3-aminocarbonylphenyl)-boronic acid (42 mg, 0.25 mmol) in 0.4 M sodium carbonate
aqueous solution (1.3 mL) and acetonitrile (1.3 mL) was added PPh₃ (15 mg, 0.01 mmol).

After stirring at about 90°C under N₂ for 12 hours, the reaction mixture is partitioned between
saturated NaHCO₃ and CHCl₃/2-propanol (4/1). The aqueous layer is extracted with
additional CHCl₃/2-propanol (4/1) and the combined organic layers are dried over MgSO₄,
filtered, and concentrated under reduced pressure. The resultant yellowish oil is purified by
column chromatography (SiO₂, ethyl acetate) to give

3-[6-(4-trifluoromethoxyphenyl-amino)-pyrimidin-4-yl]-benzamide as a white solid (82 mg;
88%). MS m/z 375.10 (M⁺1).

[0111] Example 7. [6-(3-Amino-phenyl)-pyrimidin-4-yl]-
(4-trifluoromethoxy-phenyl)-amine

![Chemical Structure](image)

[0112] To a degassed solution of (6-chloropyrimidin-4-yl)-
(4-trifluoromethoxyphenyl)-amine (217 mg, 0.75 mmol), prepared as in Reference 1, and
(2-aminophenyl)-boronic acid (130 mg, 0.75 mmol) in 0.4 M sodium carbonate aqueous
solution (3.8 mL) and acetonitrile (3.8 mL) is added PPh₃ (45 mg, 0.04 mmol). The reaction mixture is stirred at about 90°C under N₂ for 12 hours and the hot suspension is filtered. The filtrate is concentrated under reduced pressure to give a crude product, which is purified by column chromatography (SiO₂, hexane/ethyl acetate (4/1)) to give

[6-(3-aminophenyl)-pyrimidin-4-yl]-(4-trifluoro-methoxyphenyl)-amine as a pale yellowish solid (218 mg; 84%). MS m/z 347.10 (M⁺+1).

[0113] Example 8. N-(2-Hydroxy-ethyl)-4-[4-(4-trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzamide

![Chemical Structure]

[0114] 4-[4-(4-Trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzoic acid (50 mg; 0.13 mmol), prepared as in Reference 3, is mixed with ethanol-amine (12 µl; 0.2 mmol), HATU (54 mg, 1.5 mmol) in dry DMF (0.5 ml) and DIEA (113 µl; 0.65 mmol). The reaction is carried out at room temperature, overnight. After removing solvent, the final product is purified by reverse phase HPLC, 5-95% acetonitrile in 10 minutes to give N-(2-hydroxy ethyl)-4-[4-(4-trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzamide. MS: m/z 420.1 (M+H)⁺; ¹H NMR (400MHz, DMSO) δ 10.52 (s, 1H), 8.84 (s, 1H), 8.55 (t, J = 6.0 Hz, 1H), 8.40(d, J = 8.1 Hz, 2H), 7.98(d, J = 9.5 Hz, 2H), 7.86 (s, 2H), 7.36 (d, J = 8.0 Hz, 2H), 3.62 (s, 1H), 3.47(t, J = 6 Hz, 2H), 3.31(dd, J = 5.9, 2H).


![Chemical Structure]

[0116] 4-[4-(4-Trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzoic acid (50 mg, 0.13 mmol), prepared as in Reference 3, is mixed with N,N-dimethyl-ethane-1,2-diamine (22 µl; 0.2 mmol), HATU (54 mg; 1.5 mmol) in 0.5 ml dry
DMF and DIEA (113 μl, 0.65 mmol). The reaction is carried out at room temperature, overnight. After removing solvent, the final product is purified by reverse phase HPLC, 5-95% acetonitrile in 10 minutes, to give N-(2-Dimethylamino-ethyl)-4-[4-(4-
trifluoromethoxy-phenylamino)-[1,3,5]triazin-2-yl]-benzamide. MS: m/z 447.2 (M+H)+; 1H
NMR (400MHz, DMSO) δ 10.52 (s, 1H), 9.32 (S, 1H), 8.84 (s, 1H), 8.79 (t, J = 4.5 Hz, 1H), 8.42 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.86 (s, 2H), 7.35 (d, J = 8.0 Hz, 2H), 3.58 (dd, J = 5.8 Hz, 2H), 3.24 (dd, J = 5.9, 2H), 2.81 (d, J = 4.8).

[0117] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Examples 10-14 and Table 1, are obtained.

[0118] Example 10. N-(2-Morpholin-4-yl-ethyl)-N'-[4-trifluoromethoxy-phenyl]-pyrimidine-4,6-diamine

![Chemical Structure](image)

[0119] White solid. MS: m/z 384.2 (M+H)+; 1H NMR (400MHz, CDCl3) δ

8.21 (s, 1H), 7.76 (s, 1H), 7.34 (d, J=8.2Hz, 2H), 7.20 (d, J=8.4Hz, 2H), 5.89 (s, 1H), 3.69 (t, J=4.7Hz, 4H), 2.27 (d, J=4.3Hz, 2H), 2.58 (t, J=5.2Hz, 2H), 2.45 (t, J=5.3Hz, 4H).

[0120] Example 11. (6-Imidazol-1-yl-pyrimidin-4-yl)-(4-trifluoromethoxy-phenyl)-amine

![Chemical Structure](image)

[0121] White solid. MS: m/z 322.1 (M+H)+; 1H NMR (400MHz, DMSO) δ

9.15 (s, 1H), 8.67 (s, 1H), 8.12 (s, 1H), 7.77 (d, J=7.2Hz, 2H), 7.51 (s, 1H), 7.40 (d, J=8.2Hz, 2H), 7.05 (s, 1H).

[0122] Example 12. (6-[2-(3-Imidazol-1-yl-propylamino)-pyridin-4-yl]-pyrimidin-4-yl)-(4-trifluoromethoxy-phenyl)-amine
[0123] Yellow solid. MS: m/z 456.2 (M+H)^+, ¹H NMR (400MHz, DMSO) δ 9.13 (s, 1H), 8.78 (s, 1H), 8.12 (d, J=6.1Hz, 1H), 7.84 (d, J=7.2Hz, 2H), 7.81 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.37 (d, J=8.5Hz, 2H), 7.32 (s, 1H), 7.16 (d, J=5.9Hz, 1H), 4.30 (t, d=6.7Hz, 2H), 3.36 (t, J=6.8Hz, 2H), 2.16 (m, 2H).

[0124] Example 13. 3-[(6-(4-Trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-benzenesulfonamide

[0125] Pale yellow solid. MS: m/z 411.1 (M+H)^+, ¹H NMR (400MHz, DMSO) δ 8.79 (s, 1H), 8.53 (s, 1H), 8.23 (d, J=8.5Hz, 1H), 7.96 (d, J=5.1Hz, 1H), 7.85 (d, J=6.9Hz, 2H), 7.75 (t, J=7.9Hz, 1H), 7.48 (s, 2H), 7.36 (d, J=8.2Hz, 2H), 7.33 (s, 1H).

[0126] Example 14. N-(2-Hydroxy-ethyl)-4-[(4-(6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-pyridin-2-yl]-benzamide

[0127] Pale yellow solid. MS: m/z 496.2 (M+H)^+, ¹H NMR (400MHz, DMSO) δ 8.88 (d, J=5.1Hz, 1H), 8.85 (s, 1H), 8.55 (s, 2H), 8.25 (d, J=8.4Hz, 2H), 8.02(d, 8.5Hz, 2H), 7.96 (dd, J=5.2Hz, 1H), 7.87 (d, J=8.7Hz, 2H), 7.58(m, 2H), 7.49 (s, 1H), 7.38 (d, J=8.5Hz, 2H), 3.54 (t, J=6.1Hz, 2H), 3.37 (m, 2H).
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B. Assays

[0128] Compounds of the present invention are assayed to measure their capacity to selectively inhibit cell proliferation of 32D cells expressing Bcr-abl (32D-p210) compared with parental 32D cells. Compounds selectively inhibiting the proliferation of these Bcr-abl transformed cells are tested for anti-proliferative activity on Ba/F3 cells expressing either wild type or the mutant forms of Bcr-abl.

**Inhibition of cellular Bcr-abl dependent proliferation (High Throughput method)**

[0129] The murine cell line used is the 32D hemopoietic progenitor cell line transformed with Bcr-abl cDNA (32D-p210). These cells are maintained in RPMI/10% fetal calf serum (RPMI/FCS) supplemented with penicillin 50 μg/mL, streptomycin 50 μg/mL and L-glutamine 200 mM. Untransformed 32D cells are similarly maintained with the addition of 15% of WEHI conditioned medium as a source of IL3.

[0130] 50 μl of a 32D or 32D-p210 cells suspension are plated in Greiner 384 well microplates (black) at a density of 5000 cells per well. 50nl of test compound (1 mM in DMSO stock solution) is added to each well (STI571 is included as a positive control). The cells are incubated for 72 hours at 37°C, 5% CO₂. 10 μl of a 60% Alamar Blue solution (Tek diagnostics) is added to each well and the cells are incubated for an additional 24 hours. The fluorescence intensity (Excitation at 530 nm, Emission at 580 nm) is quantified using the Acquest™ system (Molecular Devices).
Inhibition of cellular Bcr-abl dependent proliferation

[0131] 32D-p210 cells are plated into 96 well TC plates at a density of 15,000 cells per well. 50 μL of two fold serial dilutions of the test compound (C_{max} is 40 μM) are added to each well (STI571 is included as a positive control). After incubating the cells for 48 hours at 37°C, 5% CO₂, 15 μL of MTT (Promega) is added to each well and the cells are incubated for an additional 5 hours. The optical density at 570nm is quantified spectrophotometrically and IC_{50} values, the concentration of compound required for 50% inhibition, determined from a dose response curve.

Effect on cell cycle distribution

[0132] 32D and 32D-p210 cells are plated into 6 well TC plates at 2.5x10⁶ cells per well in 5 ml of medium and test compound at 1 or 10 μM is added (STI571 is included as a control). The cells are then incubated for 24 or 48 hours at 37°C, 5% CO₂. 2 ml of cell suspension is washed with PBS, fixed in 70% EtOH for 1 hour and treated with PBS/EDTA/RNase A for 30 minutes. Propidium iodide (Cf= 10 μg/ml) is added and the fluorescence intensity is quantified by flow cytometry on the FACSscalibur™ system (BD Biosciences). Test compounds of the present invention demonstrate an apoptotic effect on the 32D-p210 cells but do not induce apoptosis in the 32D parental cells.

Effect on Cellular Bcr-abl Autophosphorylation

[0133] Bcr-abl autophosphorylation is quantified with capture Elisa using a c-abl specific capture antibody and an antiphostophoysine antibody. 32D-p210 cells are plated in 96 well TC plates at 2x10⁵ cells per well in 50 μL of medium. 50 μL of two fold serial dilutions of test compounds (C_{max} is 10 μM) are added to each well (STI571 is included as a positive control). The cells are incubated for 90 minutes at 37°C, 5% CO₂. The cells are then treated for 1 hour on ice with 150 μL of lysis buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 5 mM EDTA, 1 mM EGTA and 1% NP-40) containing protease and phosphatase inhibitors. 50 μL of cell lysate is added to 96 well optiplates previously coated with anti-abl specific antibody and blocked. The plates are incubated for 4 hours at 4°C. After washing with TBS-Tween 20 buffer, 50 μL of alkaline-phosphatase conjugated anti-phosphotyrosine antibody is added and the plate is further incubated overnight at 4°C. After washing with TBS-Tween 20 buffer, 90 μL of a luminescent substrate are added and the luminescence is quantified using the Acquest™ system (Molecular Devices). Test compounds of the invention that inhibit the proliferation of the Bcr-abl expressing cells, inhibit the cellular Bcr-abl autophosphorylation in a dose-dependent manner.
Effect on proliferation of cells expressing mutant forms of Bcr-abl

[0134] Compounds of the invention are tested for their antiproliferative effect on Ba/F3 cells expressing either wild type or the mutant forms of Bcr-abl (G250E, E255V, T315I, F317L, M351T) that confers resistance or diminished sensitivity to STI571. The antiproliferative effect of these compounds on the mutant-Bcr-abl expressing cells and on the non transformed cells were tested at 10, 3.3, 1.1 and 0.37 μM as described above (in media lacking IL3). The IC\textsubscript{50} values of the compounds lacking toxicity on the untransformed cells were determined from the dose response curves obtained as describe above.

[0135] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each Reference provided herein is incorporated by Reference in its entirety to the same extent as if each Reference was individually incorporated by Reference.
WHAT IS CLAIMED IS:

1. A compound of Formula I:

   \[ \begin{align*}
   X^1 & \text{ and } X^2 \text{ are independently selected from the group consisting of } -N= \text{ and } \\
   -CR^4=, \text{ wherein } R^4 \text{ is hydrogen or } C_{1,4}\text{alkyl;} \\
   \text{L is selected from the group consisting of a bond, } -O- \text{ and } -NR^5-, \text{ wherein } R^5 \\
   \text{is hydrogen or } C_{1,4}\text{alkyl;} \\
   R^1 \text{ is selected from the group consisting of } -X^3NR^6R^7, -X^3OR^7 \text{ and } -X^3R^7, \\
   \text{wherein } X^3 \text{ is a bond or } C_{1,4}\text{alkylene, } R^6 \text{ is hydrogen or } C_{1,4}\text{alkyl and } R^7 \text{ is selected from the} \\
   \text{group consisting of } C_{6-10}\text{aryl and } C_{5-6}\text{heteroaryl; wherein any aryl or heteroaryl is optionally} \\
   \text{substituted with 1 to 3 radicals independently selected from the group consisting of halo,} \\
   \text{amino, } C_{1,4}\text{alkyl, halo-substituted } C_{1,4}\text{alkyl, } C_{1,4}\text{alkoxy and halo-substituted } C_{1,4}\text{alkoxy;} \\
   \text{R}^2 \text{ is selected from the group consisting of } C_{1,4}\text{alkyl, } C_{1,4}\text{alkoxy and halo-substituted } C_{1,4}\text{alkoxy;} \\
   \text{R}^3 \text{ is selected from the group consisting of } C_{3,5}\text{heterocycloalkyl- } C_{6,4}\text{alkyl,} \\
   C_{5-10}\text{heteroaryl- } C_{6,4}\text{alkyl, } C_{6-10}\text{aryl- } C_{6,4}\text{alkyl and } -X^3NR^6R^8, \text{ wherein any alkyl group is} \\
   \text{optionally substituted with 1 to 3 radicals selected from the group consisting of hydroxy, halo} \\
   \text{and amino; and any aryl, heteroaryl or heterocycloalkyl is optionally substituted with 1 to 3} \\
   \text{radicals independently selected from the group consisting of halo, nitro, } C_{1,4}\text{alkyl,} \\
   \text{halo-substituted } C_{1,4}\text{alkyl, hydroxy- } C_{1,4}\text{alkyl, } C_{1,4}\text{alkoxy, halo-substituted } C_{1,4}\text{alkoxy, phenyl,} \\
   C_{3,4}\text{heterocycloalkyl, } -X^3C(O)NR^6R^8, -X^3C(O)NR^6R^9, -X^3C(O)R^9, -X^3S(O)NR^6R^8, \\
   -X^3NR^6R^9, -X^3NR^6R^8, -X^3S(O)NR^6R^8, -X^3S(O)R^8, -X^3NR^6R^9, -X^3S(O)NR^6R^8, -X^3S(O)R^9, \\
   -X^3C(O)R^8, -X^3NR^6C(O)R^8, -X^3NR^6S(O)R^8, -X^3NR^6S(O)R^9, -X^3S(O)NR^6R^8, -X^3S(O)R^9, \\
   -X^3NR^6C(O)R^9, -X^3NR^6C(O)NR^6R^8, -X^3NR^6C(O)NR^6R^9, -X^3NR^6C(O)NR^6R^8, -X^3C(O)OR^8, =NOR^8, \\
   -X^3NR^6OR^8, -X^3NR^6(CH_2)_{1-4}NR^6R^8, -X^3C(O)NR^6(CH_2)_{1-4}NR^6R^8, -X^3C(O)NR^6(CH_2)_{1-4}R^9, \\
   -X^3NR^6(CH_2)_{1-4}OR^9, -X^3O(CH_2)_{1-4}NR^6R^8, -X^3C(O)NR^6(CH_2)_{1-4}OR^8 \text{ and } \\
   X^2NR^6(CH_2)_{1-4}R^9; \text{ wherein phenyl can be further substituted by a radical selected from} \\
   \end{align*} \]

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-NR<sup>8</sup>R<sup>8</sup> or -C(O)NR<sup>8</sup>R<sup>8</sup>; X<sup>2</sup> is as described above; R<sup>8</sup> is hydrogen, C<sub>1-6</sub>alkyl, hydroxy-C<sub>1-6</sub>alkyl or C<sub>2-6</sub>alkenyl; and R<sup>9</sup> is hydroxy, C<sub>6-10</sub>aryl-C<sub>0-4</sub>alkyl, C<sub>6-10</sub>aryl-C<sub>4</sub>alkyloxy, C<sub>5-10</sub>heteroaryl-C<sub>0-4</sub>alkyl, C<sub>3-8</sub>heterocycloalkyl-C<sub>0-4</sub>alkyl or C<sub>3-8</sub>cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alky of R<sup>9</sup> is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, cyano, amino, nitro, C<sub>1-6</sub>alkyl, hydroxy-C<sub>1-6</sub>alkyl, halo-substituted C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halo-substituted C<sub>1-4</sub>alkoxy, halo-alkyl-substituted-phenyl, benzoxy, C<sub>5-9</sub>heteroaryl, C<sub>3-8</sub>heterocycloalkyl, -C(O)NR<sup>8</sup>R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>8</sup>R<sup>8</sup>, -NR<sup>8</sup>R<sup>8</sup>, -C(O)R<sup>10</sup> and -NR<sup>11</sup>R<sup>11</sup>, wherein R<sup>10</sup> is C<sub>5-9</sub>heteroaryl and R<sup>11</sup> is hydroxy-C<sub>1-4</sub>alkyl; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compounds of claim 1 of Formula Ia:

\[
\text{L}^\text{R}^3
\]

\[
\text{R}^1 \quad \text{R}^2
\]

(Ia)

in which

- L is a bond;
- R<sup>1</sup> is selected from the group consisting of -NHR<sup>7</sup>, -OR<sup>7</sup> and -R<sup>7</sup>, wherein R<sup>7</sup> is phenyl or pyridinyl, optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, amino, C<sub>1-4</sub>alkyl, halo-substituted C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy and halo-substituted C<sub>1-4</sub>alkoxy;
- R<sup>2</sup> is hydrogen or C<sub>1-4</sub>alkyl; and
- R<sup>3</sup> is C<sub>6-10</sub>aryl-C<sub>0-4</sub>alkyl, optionally substituted with 1 to 3 radicals independently selected from the group consisting of -C(O)NR<sup>8</sup>R<sup>8</sup>, -C(O)NR<sup>8</sup>R<sup>9</sup>, -C(O)R<sup>9</sup> and -C(O)NR<sup>8</sup>(CH<sub>3</sub>)<sub>2</sub>NR<sup>8</sup>R<sup>8</sup>, wherein R<sup>8</sup> is hydrogen, C<sub>1-6</sub>alkyl or hydroxy-C<sub>1-4</sub>alkyl; and R<sup>9</sup> is C<sub>3-8</sub>heterocycloalkyl-C<sub>0-4</sub>alkyl, optionally substituted by -C(O)NR<sup>8</sup>R<sup>8</sup>.

3. The compounds of claim 2 in which

- R<sup>1</sup> is -NHR<sup>7</sup>, wherein R<sup>7</sup> is phenyl substituted with halo-substituted C<sub>1-4</sub>alkyl or halo-substituted C<sub>1-4</sub>alkoxy; and
- R<sup>2</sup> is hydrogen; and
R³ is phenyl substituted with -C(O)NH(CH₂)₂OH, -C(O)NHR³, -C(O)R⁹ or
-NH(CH₂)₂N(CH₃)₂, wherein R⁹ is morpholino-ethyl or piperidinyl, substituted with
-C(O)NH₂.

4. The compounds of claim 1 of Formula Ib:

\[
\begin{array}{c}
\text{N} \\
	ext{R¹} \\
\text{N} \\
\text{R²} \\
\text{R³} \\
\text{L}
\end{array}
\]

(lb)

in which

L is a bond;

R¹ is selected from the group consisting of -NHR⁷, -OR⁷ and -R⁷, wherein R⁷
is phenyl or pyridinyl optionally substituted with 1 to 3 radicals independently selected from
the group consisting of halo, amino, C₁₄alkyl, halo-substituted C₁₄alkyl, C₁₄alkoxy and
halo-substituted C₁₄alkoxy;

R² is hydrogen or C₁₄alkyl; and

R³ is selected from C₅₋₆heteroaryl-C₀₋₄alkyl or C₆₋₁₀aryl-C₀₋₄alkyl; wherein any
aryl or heteroaryl is optionally substituted with 1 to 3 radicals selected from the group
consisting of C₃₋₅heterocycloalkyl, -C(O)NR⁸R⁹, -C(O)NR⁹R⁸, -C(O)R⁹, -NR⁸R⁹ and
-NR⁸(CH₂)₂NR⁸R⁹, wherein R⁸ is hydrogen, C₁₀₋₁₄alkyl or hydroxy-C₁₀₋₁₄alkyl; and R⁹ is
C₆₋₁₀aryl-C₀₋₄alkyl, C₅₋₁₀heteroaryl-C₀₋₄alkyl, C₃₋₅heterocycloalkyl-C₀₋₄alkyl or C₃₋₅cycloalkyl;
wherein any aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl of R⁹ is further optionally
substituted by up to 2 radicals selected from the group consisting of hydroxy, C₁₋₄alkyl,
hydroxy-C₁₋₄alkyl, C₃₋₅heterocycloalkyl, -C(O)NR⁸R⁹ and -S(O)₂NR⁸R⁹.

5. The compounds of claim 4 in which

R¹ is -NHR⁷, wherein R⁷ is phenyl substituted with halo-substituted C₁₄alkyl
or halo-substituted C₁₄alkoxy;

R² is hydrogen; and

R³ is pyridinyl or phenyl, optionally substituted with 1 to 3 radicals selected
from the group consisting of -C(O)NH(CH₂)₂OH, -C(O)NHCH(CH₃)₂CH₂OH,
-C(O)NH(CH₂)₂CH₃, -C(O)N(CH₃)₂, -C(O)NH(CH₂)₂N(CH₃)₂, -C(O)NHR⁹,
-C(O)N(C₂H₅)R⁹ and -C(O)R⁹, wherein R⁹ is phenyl, phenethyl, pyridinyl, pyrrolidinyl,
piperidinyl, morpholino or morpholino-ethyl; wherein any aryl, heteroaryl, heterocycloalkyl or alkyl of R⁹ is further optionally substituted by up to 2 radicals selected from the group consisting of hydroxy, C₁₄alkyl, -CH₂OH, -(CH₂)₂OH, pyrrolidinyl, piperazinyl, -C(O)NH₂, -C(O)N(C₂H₅)₂ and -S(O)₂NH₂.

6. The compounds of claim 1 of Formula Ic:

(Ic)

in which

L is a bond, -NH-, -N(C₂H₅)- or -O-;

R¹ is selected from the group consisting of -NHR⁷, -OR⁷ and -R⁷, wherein R⁷ is phenyl or pyridinyl, optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, amino, C₁₄alkyl, halo-substituted C₁₄alkyl, C₁₄alkoxy and halo-substituted C₁₄alkoxy; and

R² is hydrogen or C₁₄alkyl.

7. The compounds of claim 6 in which

L is a bond; and

R³ is selected from the group consisting of C₃₋₅heterocycloalkyl-C₀₋₄alkyl, C₅₋₁₀heteroaryl-C₀₋₄alkyl and C₆₋₁₀aryl-C₀₋₄alkyl; wherein any aryl, heteroaryl or heterocycloalkyl is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, nitro, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, C₃₋₅heterocycloalkyl, -X³C(O)NR⁸R⁸, -X³C(O)NR⁸R⁸, -X³SR⁸R⁸, -X³NR⁸R⁸, -X³S(O)₂NR⁸R⁸, -X³S(O)₂R⁸,

-X⁳S(O)₂R⁹, -X³C(O)R⁸, -X³NR⁸C(O)R⁸, -X³S(O)₂R⁸, -X³S(O)₂R⁹, -X³NR⁸S(O)₂R⁸, -X³NR⁸S(O)₂R⁹,

-X³NR⁸C(O)R⁹, -X³NR⁸C(O)NR⁸R⁹, -X³NR⁸S(O)₂NR⁸R⁹, -X³C(O)OR⁸, -NOR⁸,

-X⁳NR⁸C(CH₂)₄NR⁸R⁸, -X³C(O)NR⁸C(CH₂)₄NR⁸R⁸ and -X³O(CH₂)₄NR⁸R⁸; R⁸ is hydrogen, C₁₋₄alkyl or hydroxy-C₁₋₄alkyl; R⁹ is C₆₋₁₀aryl-C₀₋₄alkyl, C₆₋₁₀aryl-C₀₋₄alkoxy, C₅₋₁₀heteroaryl-C₀₋₄alkyl, C₃₋₅heterocycloalkyl-C₀₋₄alkyl or C₃₋₅cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl of R⁹ is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, halo-substituted C₁₋₄alkyl, C₁₋₄alkoxy, halo-alkyl-substituted-phenyl,
The compounds of claim 7 in which R³ is selected from the group
consisting of morpholino, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, 4-o xo-piperidin-1-yl,
piperazinyl, pyrroldinyl, pyridinyl, phenyl, naphthyl, thiophenyl, benzofuran-2-yl,
benzo[1,3]dioxolyl, piperidinyl, pyrazinyl, pyrimidinyl, imidazolyl, pyrazolyl and
1H-benzoimidazolyl; wherein any aryl, heteroaryl or heterocycloalkyl is optionally
substituted with 1 to 2 radicals independently selected from the group consisting of chloro,
 methyl, ethyl, hydroxymethyl, methoxy, -C(O)OH, -C(O)H, -C(O)OCH₃, -C(O)N(C₂H₅)₂,
 -C(O)N(CH₃)₂, -C(O)NHCH₃, -S(O)₂NH₂, -S(O)₂CH₃, chloro, -NH₂, -C(O)CH₃, =NOCH₃,
-NH(CH₂)₂N(CH₃)₂, -NH(CH₂)₂NH₂, -NH(CH₂)₂OH, -C(O)NH(CH₂)₂N(CH₃)₂, -NHR³,
-O(CH₂)₂N(CH₃)₂, morpholino, piperazinyl, -NHC(O)CH₃, -NHC(O)NHC₄H₉,
-C(O)NHC₄H₉, -C(O)NHCH₃, -C(O)NHC₄H₉, -C(O)N(C₂H₄OH)₂, -C(O)NHC₄H₉OH,
-C(O)NH(CH₂)₂OH, -NHC(O)R³, -C(O)NHR³, -NHC(O)NHR³, -C(O)R³, -NHS(O)₂C₄H₉,
-NHS(O)₂CH₃, -NHS(O)₂R³, -S(O)₂R³, -S(O)₂NHR³, -C(O)NH₂ and
-C(O)NH(CH₂)₂N(CH₃)₂; R³ is phenethyl, 2-phenoxy-ethyl, 1H-imidazolyl-propyl, pyridinyl,
pyridinyl-methyl, quinolinyl, morpholino, piperidinyl, piperazinyl, pyrroldinyl,
tetrahydro-furan-2-ylmethyl, furan-2-ylmethyl, thiazol-2-ylmethyl,
benzo[1,3]dioxol-5-ylmethyl, benzo[1,3]dioxol-5-yl, 3-(2-oxo-pyrrolidin-1-yl)-propyl,
3-imidazol-1-yl-propyl, 3H-pyrazol-3-yl, morpholino-ethyl, phenyl, thiophenyl-methyl,
benzyl, cyclohexyl or furan-2-ylmethyl; wherein said aryl, heteroaryl, cycloalkyl,
heterocycloalkyl or alkyl of R³ is further optionally substituted by up to 2 radicals selected
from hydroxy-methyl, hydroxy-ethyl, isobutyl, nitro, amino, hydroxyl, methoxy,
trifluoromethoxy, cyano, isopropyl, methyl, ethyl, chloro, fluoro, pyridinyl, morpholino,
phenoxy, pyrroldinyl, trifluoromethyl substituted-phenyl, -N(CH₃)₂,
-C(O)NH₂, -S(O)₂NH₂, -C(O)N(CH₃)₂, cyano or -C(O)R¹⁰; and R¹⁰ is furanyl.

The compounds of claim 6 in which
L is -NH₂, -N(C₂H₅)- or -O-; and
R³ is selected from the group consisting of C₅₋₁₀heteroaryl-C₉₋₄alkyl and.
C₆₋₁₀aryl-C₉₋₄alkyl; wherein any aryl or heteroaryl is optionally substituted with 1 to 3
radicals independently selected from the group consisting of C₁₋₉alkoxy,
C₃₋₄heterocycloalkyl, -X²C(O)NR⁸R⁸, -X²S(O)₂NR⁸R⁸, -X³NR⁸C(O)R⁸ and
-X₃NR₈C(O)NR₈R₈; R₈ is hydrogen or C₁₆alkyl; and R₈ is C₆-1₀aryl-C₀-₄alkyl optionally substituted by up to 2 halo-substituted C₁₄alkyl radicals.

10. The compounds of claim 9 in which R₃ is selected from the group consisting of quinolinyl, pyridinyl and phenyl; wherein any aryl or heteroaryl is optionally substituted with 1 to 2 radicals independently selected from the group consisting of morpholino, methoxy, -C(O)NH₂, -NHC(O)NHR₈ and -S(O)₂NH₂; and R₈ is phenyl substituted by trifluoromethyl.

11. A pharmaceutical composition for the treatment of tumors in warm-blooded animals, comprising an effective amount of a compound of claim 1.

12. A method of treatment of warm-blooded animals suffering from a tumoral disease, comprising treating warm-blooded animals in need of such treatment with an effective tumor-inhibiting amount of a compound of claim 1.

13. The method of claim 12, wherein said tumor disease is responsive to inhibition of a tyrosine protein kinase.

14. The method of claim 13, wherein said tyrosine protein kinase is Bcr-Abl.

15. A method of inhibiting Bcr-abl activity, the method comprising contacting Bcr-abl with a compound that binds to a myristoyl binding pocket of Bcr-abl.

16. The method of claim 15, wherein the compound is a compound of claim 1.

17. A process for preparing a compound of claim 1, said process comprising:

(a) reacting a compound of Formula 2 with a compound of Formula 3, 4, 5 or 6:

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R¹ N R²
\(X¹\) \(X²\) \(R³\-\text{B(OH)}_₂\) \(R³\-\text{SnBu}_₃\) \(R³\-\text{OH}\) \(R³\-\text{NR₈H}\)
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(2)
in which $X^1$, $X^2$, $R^1$, $R^2$, $R^3$ and $R^5$ are as defined for Formula I above and Q represents a fluoro, chloro, bromo or iodo; or
(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;
(c) optionally converting a salt form of a compound of the invention to a non-salt form;
(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;
(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;
(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;
(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and
(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.