FUSED PYRROLOCARBAZOLES AND METHODS FOR THE PREPARATION THEREOF

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority of U.S. Provisional Application No. 60/532,252, filed December 23, 2003, which is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates generally to fused pyrrolocarbazoles, including pharmaceutical compositions, diagnostic kits, assay standards or reagents containing the same, and the same compounds for use as therapeutics. The invention is also directed to intermediates and processes for making these novel compounds.

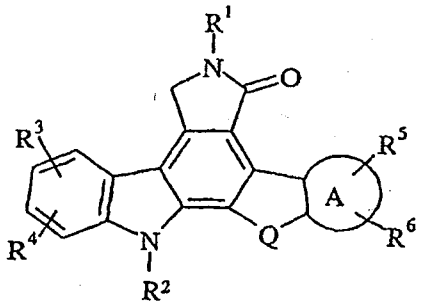
BACKGROUND OF THE INVENTION

[0003] Publications cited throughout this disclosure are incorporated in their entirety herein by reference.

[0004] Various synthetic small organic molecules that are biologically active and generally known in the art as "fused pyrrolocarbazoles" have been prepared (See U.S. Patent Nos. 5,475,110; 5,591,855; 5,594,009; 5,616,724; and 6,630,500). In addition, U.S. Patent 5,705,511 discloses fused pyrrolocarbazole compounds which possess a variety of functional pharmacological activities. The fused pyrrolocarbazoles were disclosed to be used in a variety of ways, including: enhancing the function and/or survival of cells of neuronal lineage, either singularly or in combination with neurotrophic factor(s) and/or indolocarbazoles; enhancing trophic factor-induced activity; inhibition of protein kinase C ("PKC") activity; inhibition of *trk* tyrosine kinase activity; inhibition of proliferation of a prostate cancer cell-line; inhibition of the cellular pathways involved in the inflammation process; and enhancement of the survival of neuronal cells at risk of dying. However, there remains a need for novel pyrrolocarbazole derivatives that possess beneficial properties. This invention is directed to this, as well as other important ends.

SUMMARY OF THE INVENTION

[0005] The present invention in one aspect is directed to fused pyrrolocarbazole compounds of Formula II :



II

and its stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt forms thereof, wherein the constituent members are defined *infra*.

[0006] The fused pyrrolocarbazoles of the present invention may be used in a variety of ways, including: for inhibition of angiogenesis; as antitumor agents; for enhancing the function and/or survival of cells of neuronal lineage, either singularly or in combination with neurotrophic factor(s) and/or indolocarbazoles; for enhancing trophic factor-induced activity; inhibition of kinase activity, such as *trk* tyrosine kinase ("*trk*"), vascular endothelial growth factor receptor ("VEGFR") kinase, preferably VEGFR1 and VEGFR2, mixed lineage kinase ("MLK"), dual leucine zipper bearing kinase ("DLK"), platelet derived growth factor receptor kinase ("PDGFR"), protein kinase C ("PKC"), Tie-2, or CDK-1, -2, -3, -4, -5, -6; for inhibition of NGF-stimulated *trk* phosphorylation; for inhibition of proliferation of a prostate cancer cell-line; for inhibition of the cellular pathways involved in the inflammation process; and for enhancement of the survival of neuronal cells at risk of dying. In addition, the fused pyrrolocarbazoles may useful for inhibition of c-met, c-kit, and mutated Flt-3 containing

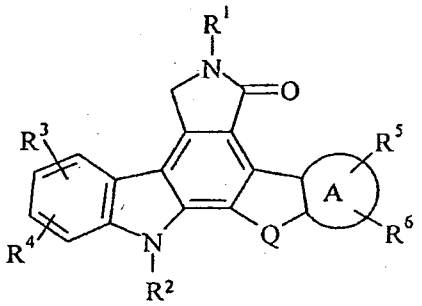
internal tandem duplications in the juxtamembrane domain. Because of these varied activities, the disclosed compounds find utility in a variety of settings, including research and therapeutic environments.

[0007] In other embodiments, the compounds of the present invention are useful for treating or preventing angiogenesis and angiogenic disorders such as cancer of solid tumors, endometriosis, retinopathy, diabetic retinopathy, psoriasis, hemangioblastoma, ocular disorders or macular degeneration. In another embodiment, the compounds of the present invention are useful for treating or preventing neoplasia, rheumatoid arthritis, chronic arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, atherosclerosis, or restenosis. In further embodiments, the compounds of the present invention are useful for treating or preventing neurodegenerative diseases and disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, stroke, ischemia, Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathy, chemotherapy induced peripheral neuropathy, AIDS related peripheral neuropathy, or injuries of the brain or spinal chord. In additional embodiments, the compounds of the present invention are useful for treating or preventing prostate disorders such as prostate cancer or benign prostate hyperplasia. In still other embodiments, the compounds of the present invention are useful for treating or preventing multiple myeloma and leukemias including, but not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia.

[0008] In further aspect, the present invention is directed to pharmaceutical compositions which comprises one or more pharmaceutically acceptable excipients and a therapeutically effective amount of a compound of the present invention.

DETAILED DESCRIPTION

[0009] Thus, in a first embodiment, the present invention provides a novel compound of Formula II :



II

or a stereoisomer or a pharmaceutically acceptable salt thereof wherein:

ring A together with the carbon atoms to which it is attached, is a phenylene ring in which from 1 to 3 carbon atoms may be replaced by nitrogen atoms;

R^1	is H or optionally substituted alkyl, wherein said optional substituents are one to three R^{10} groups;
R^2	is selected from H, $C(=O)R^{2a}$, $C(=O)NR^{2C}R^{2d}$, SO_2R^{2b}, CO_2R^{2b}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{3-10} cycloalkyl and optionally substituted heterocycloalkyl, wherein said optional substituents are one to three R^{10} groups;
R^{2a}	is selected from optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, OR^{2b} $NR^{2c}R^{2d}$, $(CH_2)_pNR^{2c}R^{2d}$, and $O(CH_2)_pNR^{2c}R^{2d}$, wherein said optional substituents are one to three R^{10} groups;
R^{2b}	is selected from H and optionally substituted C_{1-8} alkyl, wherein said optional substituents are one to three R^{10} groups;
R^{2c} and R^{2d}	are each independently selected from H and optionally substituted C_{1-8} alkyl, or together with the nitrogen to which they are attached form an optionally substituted heterocycloalkyl, wherein said optional substituents are one to three R^{10} groups;

at least one of R^3, R^4, R^5, and R^6 is selected from the group consisting of OR^{14}; $C(=O)R^{22}$; $CH=NR^{26}$; $NR^{11}C(=O)$

R^{20}; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$; $OC(=O)NR^{11}R^{20}$; O-(C_{1-8} alkylene)-R^{24}; Z^1-(C_{1-8} alkylene)-R^{23}, wherein Z^1 is selected from CO_2, O_2C, C(=O), $NR^{11}C(=O)$, and $NR^{11}C(=O)O$; and (C_{1-8} alkylene)-Z^2-(C_{1-8} alkylene)-R^{23}, wherein Z^2 is selected from O, $S(O)_y$, $C(=O)NR^{11}$, $NR^{11}C(=O)$, $NR^{11}C(=O)NR^{11}$, $OC(=O)NR^{11}$ and $NR^{11}C(=O)O$, wherein said alkylene groups are optionally substituted with one to three R^{10} groups;
the other R^3, R^4, R^5, and R^6 moieties can be independently selected from the group consisting of H, R^{10}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl and optionally substituted C_{2-8} alkynyl, wherein said optional substitutents are one to three R^{10} groups;
Q is $-CH_2-CH_2-$;;

R^{10} is selected from C_{1-8} alkyl, C_{3-10} cycloalkyl, C_{3-10} spirocycloalkyl, C_{6-12} aryl, heteroaryl , heterocycloalkyl , C_{6-10} arylalkoxy, F, Cl, Br, I, CN, CF_3, $NR^{27A}R^{27B}$, NO_2, OR^{25}, OCF_3, =O, $=NR^{25}$, =N-OR^{25}, =N-$N(R^{25})_2$, $OC(=O)NHR^{11}$, O-$Si(R^{16})_4$, O-tetrahydropyranyl, ethylene oxide, $NR^{16}C(=O)R^{25}$, $NR^{16}CO_2R^{25}$, $NR^{16}C(=O)NR^{27A}R^{27}B$, NHC(=NH)NH2, $NR^{16}S(O)_2R^{25}$, S(O) yR^{25}, CO_2R^{25}, $C(=O)NR^{27A}R^{27B}$ $C(=O)R^{25}$, CH_2OR^{25}, $(CH_2)pOR^{25}$, $CH=NNR^{27A}R^{27B}$, $CH=NOR^{25}$, $CH=NR^{25}$, $CH=NNHCH(N=NH)NH_2$, $S(=O)_2NR^{27A}R^{27B}$, P(=O)(OR^{25})2, OR^{13}, and a monosaccharide wherein each hydroxyl group of the monosaccharide is independently either unsubstituted or is replaced by H, C_{1-8} alkyl, C_{1-8} alkylcarbonyloxy, or C_{1-8} alkoxy;

R^{11} is selected from H and optionally substituted C_{1-8} alkyl, wherein said optional substituents are one to three R^{10} groups;

R^{12} is selected from optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, and optionally substituted heteroaryl. , wherein said optional substituents are one to three R^{10} groups;

R^{13} is the residue of an amino acid after the removal of the hydroxyl moeity from the carboxyl group thereof;

R^{14} is a substituted heteroaryl, wherein said substituents is one to three R^{10} groups;

R^{15} is optionally substituted C_{1-8} alkyl, wherein said optional substituents is one to three R^{10} groups;

R^{16} is H or C_{1-8} alkyl;

R^{17} is selected from optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl,optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, wherein said optional substituents are one to three R^{10} groups;

R^{18} is selected from H, optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl, optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, , wherein said optional substituents are one to three R^{10} groups;

R^{19} is selected from optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocycloalkyl, , and optionally substituted heteroaryl, , wherein said optional substituents are one to three R^{10} groups;

R^{20} is selected from substituted C_{6-12} aryl, substituted heteroaryl , optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, wherein said substituents are one to three R^{10} groups;

R^{21} is selected from substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, substituted C_{6-12} aryl, substituted arylalkyl, substituted heteroaryl , optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, wherein said substituents are one to three R^{10} groups;

R^{22} is an substituted C_{6-12} aryl, substituted heteroaryl , wherein said substituents are one to three R^{10} groups;

R^{23} is selected from optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl, , optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocycloalkyl, , OR^{21}, $O(CH_2)_pOR^{21}$, $(CH_2)_pOR^{21}$, SR^{18}, SOR^{17}, SO_2R^{18}, CN, $N(R^{20})_2$, $CHOH(CH_2)_pN(R^{11})_2$, $C(=O)N(R^{18})_2$, $NR^{18}C(=O)R^{18}$, $NR^{18}C(=O)N(R^{18})_2$, $C(=NR^{18})OR^{18}$, $C(R^{12})=NOR^{18}$, $NHOR^{21}$, $NR^{18}C(=NR^{18})N(R^{18})_2$, NHCN, $CONR^{18}OR^{18}$, CO_2R^{18}, $OCOR^{17}$, $OC(=O)N(R^{18})_2$, $NR^{18}C(=O)OR^{17}$, and $C(=O)R^{18}$, wherein said optional substituents are one to three R^{10} groups;

R^{24} is selected from optionally substituted C_{2-8} alkenyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl, , optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocycloalkyl, CN, OR^{21}, $O(CH_2)_pOR^{21}$, $(CH_2)_pOR^{21}$, SR^{19}, SOR^{17}, SO_2R^{18}, $CHOH(CH_2)_pN(R^{11})_2$, $NR^{18}C(=O)R^{18}$, $NR^{18}C(=O)N(R^{18})_2$, $C(=NR^{18})OR^{18}$, $NHOR^{21}$, $NR^{18}C(=NR^{18})N(R^{18})_2$, NHCN, $C(O)N(R^{18})_2$, $C(=O)NR^{27A}R^{27B}$, $C(=O)NR^{11}R^{28}$, $C(=O)NR^{18}OR^{18}$, $C(=O)NR^{11}N(R^{11})_2$, C(=O) NR^{11}(alkylene)$NR^{27A}R^{27B}$, CO_2R^{18}, $OCOR^{17}$, $OC(=O)N(R^{18})_2$, $NR^{18}C(=O)OR^{17}$, C(=O) $NR^{11}R^{18}$ and $C(=O)R^{18}$, wherein said optional substituents are one to three R^{10} groups;

R^{25}	is H, C_{1-8} alkyl, C_{6-12} aryl, heteroaryl, C_{3-10} cycloalkyl, or heterocycloalkyl;
R^{26}	is selected from optionally substituted C_{3-10} cycloalkyl and optionally substituted heterocycloalkyl, , wherein said optional substituents are one to three R^{10} groups;
R^{27A} and R^{27B}	are each independently selected from H and C_{1-8} alkyl, or together with the nitrogen to which they are attached form an optionally substituted heterocycloalkyl , wherein said optional substituents are selected from C_{1-8} alkyl, C_{6-12} aryl and heteroaryl;

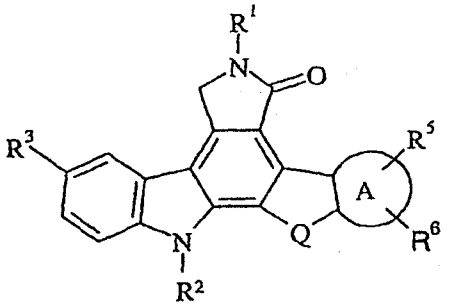
wherein heterocycloalkyl refers to a saturated or partially saturated mono- or bicyclic alkyl ring system containing 3 to 10 carbon atoms in which one or more ring carbon atoms are replaced by at least one hetero atom such as -O-, -N-, or -S-;
and wherein heteroaryl refers to an aryl group containing 5 to 10 ring carbon atoms in which one or more carbon atoms are replaced by at least one hetero atom such as -O-, -N-, or -S-;

R^{28} is optionally substituted arylalkyl, wherein said optional substituent is one to three R^{10} groups;

p is independently selected from 1,2,3, and 4;
y is independently selected from 0, 1 and 2; and
a stereoisomer or a pharmaceutically acceptable salt form thereof.

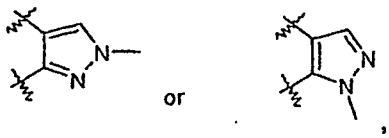
[0010] Other aspects of the present invention include those compounds wherein R^2 is preferably H, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, or optionally substituted C_{3-10} cycloalkyl, and more preferably R^2 is H or optionally substituted C_{1-8} alkyl. Further aspects include those compounds wherein R^{14} is benzoxazole, benzothiazole, pyrimidine, pyrazine or triazine; R^{22} is a 5-membered heteroaryl group; R^{20} is heterocycloalkyl or heteroaryl; R^{23} is heteroaryl or heterocycloalkyl; R^{24} is heteroaryl; and R^{26} is heterocycloalkyl. Additional aspects of the present invention include any combination of the above preferred substituents, such as, for example, a compound of Formula I with the preferred moieties of groups R^1 and R^2; or R^1, R^2; etc.

[0011] In yet another embodiment of the present invention, there are included compounds having a structure of Formula III:

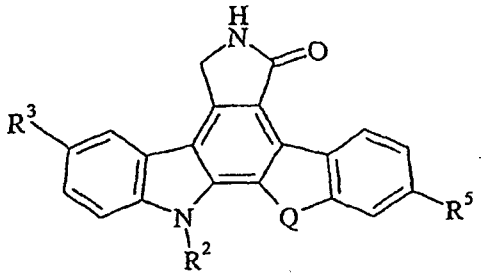


III

where preferrably ring A is phenylene or pyrazolylene, preferably



and R^1 is H or alkyl;
and Formula IV:



IV ;

[0012] In certain aspects of the present invention, there are included compounds of Formulas III-IV, wherein R^2 is H, $C(=O)R^{20}$, $C(=O)NR^{2c}R^{2d}$, SO_2R^{2b}, CO_2R^{2b}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, or optionally substituted cycloalkyl, and preferably H, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substitued C_{2-8} alkynyl, or optionally substituted cycloalkyl, and more preferable R^2 is H or optionallyl-substituted C_{1-8} alkyl. Q is CH_2CH_2. Additional aspects of the present invention include any combination of the above preferred substituents for each of Formulas III-IV.

[0013] The following paragraphs show additional aspects of the invention for at least one R^3, R^4, R^5, and R^6 for compounds of Formulas I-VI and their respective preferred embodiments described heretofore.

1. OR^{14}; paticularly those wherein R^{14} is optionally substituted benzoxazole, optionally substituted benzothiazole, optionally substituted pyrimidine, optionally substituted pyrazine or optionally substituted triazine.
2. $C(=O)R^{22}$; paticularly those wherein R^{22} is an optionally substituted 5-membered heteroaryl group.
3. $CH=NR^{26}$; paticularly those wherein R^{26} is optionally substituted heterocycloalkyl.
4. $NR^{11}C(=O)R^{20}$; paticularly those wherein R^{20} is optionally substituted heteroaryl.
5. $NR^{11}C(=O)OR^{15}$.
6. $OC(=O)R^{20}$; paticularly those wherein R^{20} is optionally substituted heterocycloalkyl.
7. $OC(=O)NR^{11}R^{20}$; paticularly those wherein R^{20} is optionally substituted cycloalkyl or optionally substituted heterocycloalkyl.
8. O-(alkylene)-R^{24}; paticularly those wherein R^{24} is optionally substituted heterocycloalkyl
9. Z^1-(C_{2-8} alkylene)-R^{23}, wherein Z^1 is selected from CO_2, O_2C, C(=O), NR^{11}, $NR^{11}C(=O)$, and $NR^{11}C(=O)O$; paticularly those wherein Z^1 is C(=O) or NR^{11}.
10. (C_{2-8} alkylene)-Z^2-(C_{2-8} alkylene)-R^{23}, wherein Z^2 is selected from O, $S(O)_y$, $C(=O)NR^{11}$, $NR^{11}C(=O)$, $NR^{11}C(=O)NR^{11}$, $OC(=O)NR^{11}$, $NR^{11}C(=O)O$; paticularly those wherein Z^2 is O, $C(=O)NR^{11}$, or $NR^{11}C(=O)$.

[0014] The preceding paragraphs may be combined to further define additional prefered embodiments of compounds of Formulas II-IV. For example, one such combination for R^3, R^4, R^5, or R^6 can include OR^{14}; $C(=O)R^{22}$; $NR^{11}C(=O)R^{20}$; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$; or $OC(=O)NR^{11}R^{20}$.

[0015] Another such combination includes OR^{14}; $C(=O)R^{22}$; and $NR^{11}C(=O)OR^{15}$.

[0016] A third such combination includes OR^{14}, wherein R^{14} is benzoxazole, benzothiazole, pyrimidine, pyrazine or triazine; $C(=O)R^{22}$, wherein R^{22} is a 5-membered heteroaryl group; $NR^{11}C(=O)R^{20}$, wherein R^{20} is heteroaryl; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$, wherein R^{20} is heterocycloalkyl; or $OC(=O)NR^{11}R^{20}$, wherein R^{20} is cycloalkyl, wherein each R^{14}, R^{22}, and R^{20} is optionally substituted as set forth above.

[0017] The following terms and expressions used herein have the indicated meanings.

[0018] In the formulas described and claimed herein, it is intended that when any symbol appears more than once in a particular formula or substituent, its meaning in each instance is independent of the other.

[0019] As used herein, the term "about" refers to a range of values from ± 10% of a specified value. For example, the phrase "about 50 mg" includes ± 10% of 50, or from 45 to 55 mg.

[0020] As used herein, a range of values in the form "x-y" or "x to y", or "x through y", include integers x, y, and the integers therebetween. For example, the phrases "1-6", or "1 to 6" or "1 through 6" are intended to include the integers 1, 2, 3, 4, 5, and 6. Preferred embodiments include each individual integer in the range, as well as any subcombination of integers. For example, preferred integers for "1-6" can include 1, 2, 3, 4, 5, 6, 1-2, 1-3, 1-4, 1-5, 2-3, 2-4, 2-5, 2-6, etc.

[0021] As used herein "stable compound" or "stable structure" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent. The present invention is directed only to stable compounds.

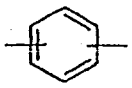
[0022] As used herein, the term "alkyl" refers to a straight-chain, or branched alkyl group having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, 1-ethylpropyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, hexyl, octyl, etc. The alkyl moiety of alkyl-containing groups, such as alkoxy, alkoxycarbonyl, and alkylaminocarbonyl groups, has the same meaning as alkyl defined above. Lower alkyl groups, which are preferred, are alkyl groups as defined above which contain 1 to 4 carbons. A designation such as "C_1-C_4 alkyl" refers to an alkyl radical containing from 1 to 4 carbon atoms.

[0023] As used herein, the term "alkenyl" refers to a straight chain, or branched hydrocarbon chains of 2 to 8 carbon atoms having at least one carbon-carbon double bond. A designation "C_2-C_8 alkenyl" refers to an alkenyl radical containing from 2 to 8 carbon atoms. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, 2,4-pentadienyl, etc.

[0024] As used herein, the term "alkynyl" refers to a straight chain, or branched hydrocarbon chains of 2 to 8 carbon atoms having at least one carbon-carbon triple bond. A designation "C_2-C_8 alkynyl" refers to an alkynyl radical containing from 2 to 8 carbon atoms. Examples include ethynyl, propynyl, isopropynyl, 3,5-hexadiynyl, etc.

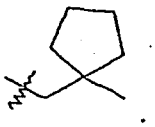
[0025] As used herein, the term "alkylene" refers to a branched or straight chained hydrocarbon of 1 to 8 carbon atoms, which is formed by the removal of two hydrogen atoms. A designation such as "C_1-C_4 alkylene" refers to an alkylene radical containing from 1 to 4 carbon atoms. Examples include methylene (-CH_2-), propylidene (CH_3CH_2CH=), 1,2-ethandiyl (-CH_2CH_2-), etc.

[0026] As used herein, the term "phenylene" refers to a phenyl group with an additional hydrogen atom removed, ie. a moiety with the structure of:



[0027] As used herein, the term "cycloalkyl" refers to a saturated or partially saturated mono- or bicyclic alkyl ring system containing 3 to 10 carbon atoms. A designation such as "C_5-C_7 cycloalkyl" refers to a cycloalkyl radical containing from 5 to 7 ring carbon atoms. Preferred cycloalkyl groups include those containing 5 or 6 ring carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, etc.

[0028] As used herein, the term "spirocycloalkyl" refers to a cycloalkyl group bonded to a carbon chain or carbon ring moiety by a carbon atom common to the cycloalkyl group and the carbon chain or carbon ring moiety. For example, a C_3 alkyl group substituted with an R group wherein the R group is spirocycloalkyl containing 5 carbon atoms refers to:



[0029] As used herein, the term "aryl" refers to a mono- or bicyclic hydrocarbon aromatic ring system having 6 to 12 ring carbon atoms. Examples include phenyl and naphthyl. Preferred aryl groups include phenyl or naphthyl groups. Included within the definition of "aryl" are fused ring systems, including, for example, ring systems in which an aromatic ring is fused to a cycloalkyl ring. Examples of such fused ring systems include, for example, indane and indene.

[0030] As used herein, the terms "heterocycle", "heterocyclic" or "heterocyclyl" refer to a mono- di-, tri- or other multicyclic aliphatic ring system that includes at least one heteroatom such as O, N, or S. The nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen may be optionally substituted in non-aromatic rings. Heterocycles are intended to include heteroaryl and heterocycloalkyl groups.

[0031] Some heterocyclic groups containing one or more nitrogen atoms include pyrrolidine, pyroline, pyrazoline, piperidine, morpholine, thiomorpholine, N-methylpiperazine, indole, isoindole, imidazole, imidazoline, oxazoline, oxazole, triazole, thiazoline, thiazole, isothiazole, thiadiazole, triazine, isoxazole, oxindole, pyrazole, pyrazolone, pyrimidine, pyrazine, quinoline, iosquinoline, and tetrazole groups. Some heterocyclic groups formed containing one or more oxygen atoms include furan, tetrahydrofuran, pyran, benzofurans, isobenzofurans, and tetrahydropyran groups. Some heterocyclic groups containing one or more sulfur atoms include thiophene, thianaphthene, tetrahydrothiophene, tetrahydrothiapyran, and benzothiophenes.

[0032] As used herein, the term "heterocycloalkyl" refers to a cycloalkyl group in which one or more ring carbon atoms

are replaced by at least one hetero atom such as -O-, -N-, or -S-, and includes ring systems which contain a saturated ring group bridged or fused to one or more aromatic groups. Some heterocycloalkyl groups containing both saturated and aromatic rings include phthalamide, phthalic anhydride, indoline, isoindoline, tetrahydroisoquinoline, chroman, isochroman, and chromene.

[0033] As used herein, the term "heteroaryl" refers to an aryl group containing 5 to 10 ring carbon atoms in which one or more ring carbon atoms are replaced by at least one hetero atom such as -O-, -N-, or -S-. Some heteroaryl groups of the present invention include pyridyl, pyrimidyl, purinyl, pyrrolyl, pyridazinyl, pyrazinyl, triazinyl, imidazolyl, triazolyl, tetrazolyl, indolyl, isoindolyl, quinolyl, isoquinolyl, qunioxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzoimidazolyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, isoxazolyl, naphthyridinyl, oxindolyl, and benzothiazolyl groups.

[0034] As used herein, the term "arylalkyl" refers to an alkyl group that is substituted with an aryl group. Examples of arylalkyl groups include, but are not limited to, benzyl, phenethyl, benzhydryl, diphenylmethyl, triphenylmethyl, diphenylethyl, naphthylmethyl, etc.

[0035] As used herein, the term "arylalkoxy" refers to an aryl-substituted alkoxy group, such as benzyloxy, diphenylmethoxy, triphenylmethoxy, phenylethoxy, diphenylethoxy, etc.

[0036] As used herein, the term "monosaccharide" refers to a simple sugar of the formula $(CH_2O)_n$. The monosaccharides can be straight-chain or ring systems, and can include a saccharose unit of the formula -CH(OH)-C(=O)-. Examples of monosaccharides include erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythulose, ribulose, xyulose, psicose, fructose, sorbose, tagatose, erythropentulose, threopentulose, glycerotetrulose, glucopyranose, fructofuranose, etc.

[0037] As used herein, the term "amino acid" refers to a group containing both an amino group and a carboxyl group. Embodiments of amino acids include α-amino, β-amino, γ-amino acids. The α-amino acids have a general formula HOOC-CH(side chain)-NH_2. The amino acids can be in their D, L or racemic configurations. Amino acids include naturally-occurring and non-naturally occurring moieties. The naturally-occurring amino acids include the standard 20 α-amino acids found in proteins, such as glycine, serine, tyrosine, proline, histidine, glutamine, etc. Naturally-occurring amino acids can also include non-α-amino acids (such as β-alanine, γ-aminobutyric acid, homocysteine, etc.), rare amino acids (such as 4-hydroxyproline, 5-hydroxylysine, 3-methylhistidine, etc.) and non-protein amino acids (such as citrulline, ornithine, canavanine, etc.). Non-naturally occurring amino acids are well-known in the art, and include analogs of natural amino acids. See Lehninger, A. L. Biochemistry, 2nd ed.; Worth Publishers: New York, 1975; 71-77, the disclosure of which is incorporated herein by reference. Non-naturally occurring amino acids also include α-amino acids wherein the side chains are replaced with synthetic derivatives. In certain embodiments, substituent groups for the compounds of the present invention include the residue of an amino acid after removal of the hydroxyl moiety of the carboxyl group thereof; i.e., groups of formula -C(=O)CH(side chain)-NH_2. Representative side chains of naturally occurring and non-naturally occurring α-amino acids include are shown below in Table A.

Table A

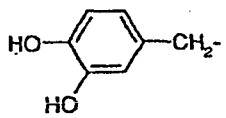
H

CH_3-

$HO-CH_2$-

$C_6H_5-CH_2$-

$HO-C_6H_4-CH_2$-



$HS-CH_2$-

$HO_2C-CH(NH_2)-CH_2-S-S-CH_2$-

CH_3-CH_2-

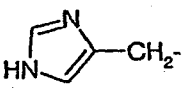
$CH_3-S-CH_2-CH_2$-

$CH_3-CH_2-S-CH_2-CH_2$-

$HO-CH_2-CH_2$-

C_5H_9-

C_6H_{11}-



$C_6H_{11}-CH_2$-

$CH_3-CH(OH)$-

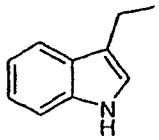
$HO_2C-CH_2-NHC(=O)-CH_2$-

HO_2C-CH_2-

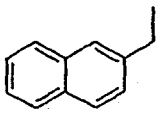
$HO_2C-CH_2-CH_2$-

$NH_2C(=O)-CH_2$-

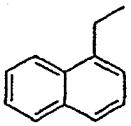
(continued)



$NH_2C(=O)-CH_2-CH_2-$
$(CH_3)_2-CH-$
$(CH_3)_2-CH-CH_2-$



$CH_3-CH_2-CH_2-$
$H_2N-CH_2-CH_2-CH_2-$
$H_2N-C(=NH)-NH-CH_2-CH_2-CH_2-$



$H_2N-C(=O)-NH-CH_2-CH_2-CH_2-$
$CH_3-CH_2-CH(CH_3)-$
$CH_3-CH_2-CH_2-CH_2-$
$H_2N-CH_2-CH_2-CH_2-CH_2-$

[0038] As used herein, the term "*trk*" refers to the family of high affinity neurotrophin receptors presently comprising trk A, trk B, and trk C, and other membrane associated proteins to which a neurotrophin can bind.

[0039] As used herein, the term "VEGFR" refers to the family of high affinity vascular endothelial growth factor receptors presently comprising VEGFR1, VEGFR2, VEGFR3, and other membrane associated proteins to which a VEGF can bind.

[0040] As used herein, the term "MLK" refers to the family of high affinity mixed lineage kinases presently comprising MLK1, MLK2, MLK3, MLK4α & β, DLK, LZK, ZAK α & β, and other serine/threonine kinases classified within this family.

[0041] As used herein, the terms "enhance" or "enhancing" when used to modify the terms "function" or "survival" means that the presence of a compound of the present invention has a positive effect on the function and/or survival of a trophic factor responsive cell compared with a cell in the absence of the compound. For example, and not by way of limitation, with respect to the survival of, e.g., a cholinergic neuron, a compound of the present invention would evidence enhancement of survival of a cholinergic neuronal population at risk of dying (due to, e.g., injury, a disease condition, a degenerative condition or natural progression) when compared to a cholinergic neuronal population not presented with such a compound, if the treated population has a comparatively greater period of functionality than the non-treated population. As a further example, and again not by way of limitation, with respect to the function of, e.g., a sensory neuron, a compound of the present invention would evidence enhancement of the function (e.g. neurite extension) of a sensory neuronal population when compared to a sensory neuronal population not presented with such a compound, if the neurite extension of the treated population is comparatively greater than the neurite extension of the non-treated population.

[0042] As used herein, the terms "inhibit" or "inhibition" refer to a specified response of a designated material (e.g., enzymatic activity) is comparatively decreased in the presence of a compound of the present invention.

[0043] As used herein, the terms "cancer" or "cancerous" refer to any malignant proliferation of cells in a mammal. Examples include prostate, benign prostate hyperplasia, ovarian, breast, brain, lung, pancreatic, colorectal, gastric, stomach, solid tumors, head and neck, neuroblastoma, renal cell carcinoma, lymphoma, leukemia, other recognized malignancies of the hematopoietic systems, and other recognized cancers.

[0044] As used herein the terms "neuron", "cell of neuronal lineage" and "neuronal cell" refer to a heterogeneous population of neuronal types having singular or multiple transmitters and/or singular or multiple functions; preferably, these are cholinergic and sensory neurons. As used herein, the phrase "cholinergic neuron" means neurons of the Central Nervous System (CNS) and Peripheral Nervous System (PNS) whose neurotransmitter is acetylcholine; exemplary are basal forebrain and spinal cord neurons. As used herein, the phrase "sensory neuron" includes neurons responsive to environmental cues (e.g., temperature, movement) from, e.g., skin, muscle and joints; exemplary is a neuron from the DRG.

[0045] As used herein the term "trophic factor" refers to a molecule that directly or indirectly affects the survival or function of a trophic factor responsive cell. Exemplary trophic factors include Ciliary Neurotrophic Factor (CNTF), basic Fibroblast Growth Factor (bFGF), insulin and insulin-like growth factors (e.g., IGF-I, IGF-II, IGF-III), interferons, interleukins, cytokines, and the neurotrophins, including Nerve Growth Factor (NGF), Neurotrophin-3 (NT-3), Neurotrophin-4/5 (NT-4/5) and Brain Derived Neurotrophic Factor (BDNF).

[0046] As used herein the term "trophic factor-responsive cell" refers to a cell which includes a receptor to which a trophic factor can specifically bind; examples include neurons (e.g., cholinergic and sensory neurons) and non-neuronal

cells (e.g., monocytes and neoplastic cells).

[0047] As used herein the terms "trophic factor activity," and "trophic factor-induced activity", refer to both endogenous and exogenous trophic factors, where "endogenous" refers to a trophic factor normally present and "exogenous" refers to a trophic factor added to a system. As defined, "trophic factor induced activity" includes activity induced by (1) endogenous trophic factors; (2) exogenous trophic factors; and (3) a combination of endogenous and exogenous trophic factors.

[0048] As used herein, the term "at risk of dying" in conjunction with a biological material, e.g., a cell such as a neuron, refers to a state or condition which negatively impacts the biological material such that the material has an increased likelihood of dying due to such state or condition. For example, compounds disclosed herein can "rescue" or enhance the survival of motoneurons which are naturally at risk of dying in an *in ovo* model of programmed cell death. Similarly, for example, a neuron may be at risk of dying due to the natural aging process which occasions the death of a neuron, or due to an injury, such as a trauma to the head, which may be such that neurons and/or glia, for example, impacted by such trauma may be at risk of dying. Further, for example, a neuron may be at risk of dying due to a disease state or condition, as in the case of neurons at risk of dying as occasioned by the disease ALS. Thus, by enhancing the survival of a cell at risk of dying by use of a compound of the claimed invention is meant that such compound decreases or prevents the risk of the death of the cell.

[0049] As used herein the term "contacting" refers to directly or indirectly causing placement together of moieties, such that the moieties directly or indirectly come into physical association with each other, whereby a desired outcome is achieved. Thus, as used herein, one can "contact" a target cell with a compound as disclosed herein even though the compound and cell do not necessarily physically join together (as, for example, is the case where a ligand and a receptor physically join together), as long as the desired outcome is achieved (e.g., enhancement of the survival of the cell). Contacting thus includes acts such as placing moieties together in a container (e.g., adding a compound as disclosed herein to a container comprising cells for *in vitro* studies) as well as administration of the compound to a target entity (e.g., injecting a compound as disclosed herein into a laboratory animal for *in vivo* testing, or into a human for therapy or treatment purposes).

[0050] As used herein, a "therapeutically effective amount" refers to an amount of a compound of the present invention effective to prevent or treat the symptoms of a particular disorder.

[0051] As used herein, the term "subject" refers to a warm blooded animal such as a mammal, preferably a human, or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and conditions described herein.

[0052] As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio.

[0053] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0054] The pharmaceutically acceptable salts of the present invention can be prepared from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

[0055] As used herein, the term "unit dose" refers to a single dose which is capable of being administered to a patient, and which can be readily handled and packaged, remaining as a physically and chemically stable unit dose comprising either the active compound itself, or as a pharmaceutically acceptable composition, as described hereinafter.

[0056] As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent compound as defined in the present invention *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Prodrugs of a compound of

the present invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo,* to the parent compound. Accordingly, prodrugs include, for example, compounds of the present invention wherein a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

[0057] It is recognized that compounds of the present invention may exist in various stereoisomeric forms. As such, the compounds of the present invention include their respective diastereomers or enantiomers. The compounds are normally prepared as racemates and can conveniently be used as such, but individual diastereomers or enantiomers can be isolated or synthesized by conventional techniques if so desired. Such racemates and individual diastereomers or enantiomers and mixtures thereof form part of the present invention.

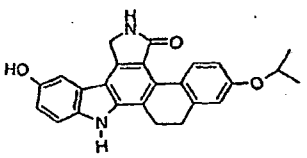
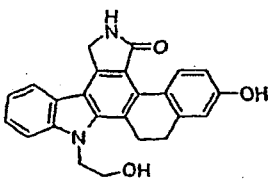
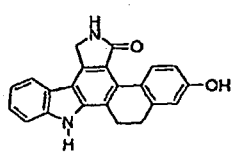
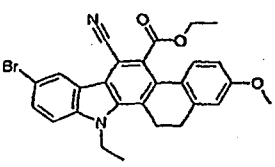
[0058] It is well known in the art how to prepare and isolate such optically active forms. Specific stereoisomers can be prepared by stereospecific synthesis using enantiomerically pure or enantiomerically enriched starting materials. The specific stereoisomers of either starting materials or products can be resolved and recovered by techniques known in the art, such as resolution of racemic forms, normal, reverse-phase, and chiral chromatography, recrystallization, enzymatic resolution, or fractional recrystallization of addition salts formed by reagents used for that purpose. Useful methods of resolving and recovering specific stereoisomers described in Eliel, E. L.; Wilen, S.H. Stereochemistry of Organic Compounds; Wiley: New York, 1994, and Jacques, J, et al. Enantiomers, Racemates, and Resolutions; Wiley: New York, 1981, each incorporated by reference herein in their entireties.

[0059] It is further recognized that functional groups present on the compounds of the present invention may contain protecting groups. For example, the amino acid side chain substituents of the compounds of the present invention can be substituted with protecting groups such as benzyloxycarbonyl or t-butoxycarbonyl groups. Protecting groups are known per se as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Preferred groups for protecting lactams include silyl groups such as t-butyldimethylsilyl ("TBDMS"), dimethoxybenzhydryl ("DMB"), acyl, benzyl, and methoxybenzyl groups. Preferred groups for protecting hydroxy groups include TBS, acyl, benzyl ("Bn"), benzyloxycarbonyl ("CBZ"), t-butyloxycarbonyl ("Boc"), and methoxymethyl. Many other standard protecting groups employed by one skilled in the art can be found in Greene, T.W. and Wuts, P.G.M., "Protective Groups in Organic Synthesis" 2d. Ed., Wiley & Sons, 1991.

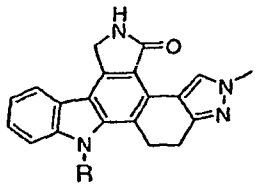
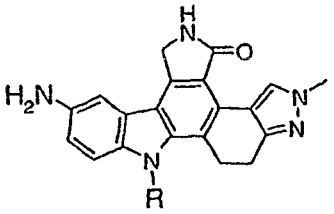
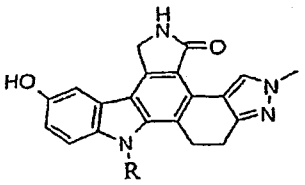
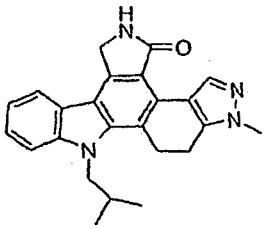
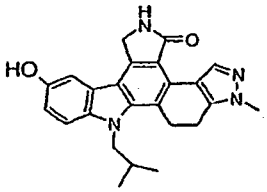
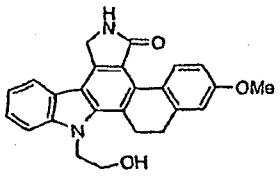
Synthesis

[0060] The general routes to prepare the examples shown in Table 1 of the present invention are shown in the Schemes 1-3. The intermediates used to prepare the examples and their mass spectral data are shown in the Table B. The reagents and starting materials are commercially available, or readily synthesized by well-known techniques by one of ordinary skill in the arts. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale. All substituents in the synthetic schemes, unless otherwise indicated, are as previously defined.

Table B

I-14 399 (M + 1)		I-18 383 (M - 1)	
I-19 339 (M - 1)		I-22 504 (M + 1)	

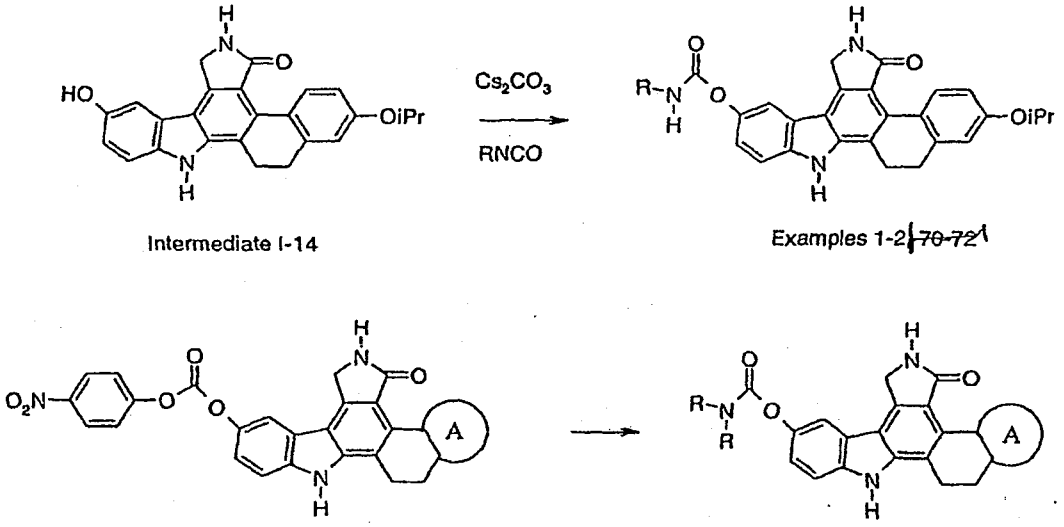
(continued)

I-23			I-29	
		R		
357 (M + 1)	23-1:	Ethyl		
371 (M + 1)	23-2:	nPropyl		R
385 (M + 1)	23-3:	i-butyl	386 (M + 1)	29-1: i-Propyl
369 (M + 1)	23-4:	allyl	386 (M + 1)	29-2: nPropyl
426 (M + 1)	23-5:	$CH_2CH_2NC_4H_8$	400 (M + 1)	29-3: i-Butyl
400 (M + 1)	23-6:	$CH_2CH_2NMe_2$	400 (M + 1)	29-4: nButyl
482 (M + 1)	23-7:	$(CH_2)_6NC_4H_8$		
I-33			1-36 385 (M+ 1)	
		R		
373 (M + 1)	33-1:	Ethyl		
401 (M + 1)	33-2:	i-Butyl		
387 (M + 1)	33-3:	i-Propyl		
387 (M + 1)	33-4:	Propyl		
I-39 401 (M + 1)			I-41 399 (M+ 1)	

[0061] The general procedures to prepare the pyrrolocarbazoles of the present invention are described in U.S. Pat. Nos. 5,705,511 ("the '511 patent") and 6,630,500, PCT Publ. No. WO 00/47583, J. Heterocyclic Chemistry, 2001, 38, 591, and J. Heterocyclic Chemistry, 2003, 40, 135. In general, the lactam nitrogen or intermediate alcohol groups of the intermediates outlined in Table B may be protected with such groups as acetyl, substituted silyl, benzyl, Boc, or dimethoxybenzhydrol.

[0062] Intermediate I-23 (wherein R is hydrogen) was prepared from the β-ketone, 2-methyl-1,4,6,7-tetrahydro-5*H*-indazol-5-one (Peet, N. P.; LeTourneau, M. E.; Heterocycles, 1991, 32, 41) using methods described in the '511 patent and in J. Heterocyclic Chemistry, 2003, 40, 35.

Scheme 1

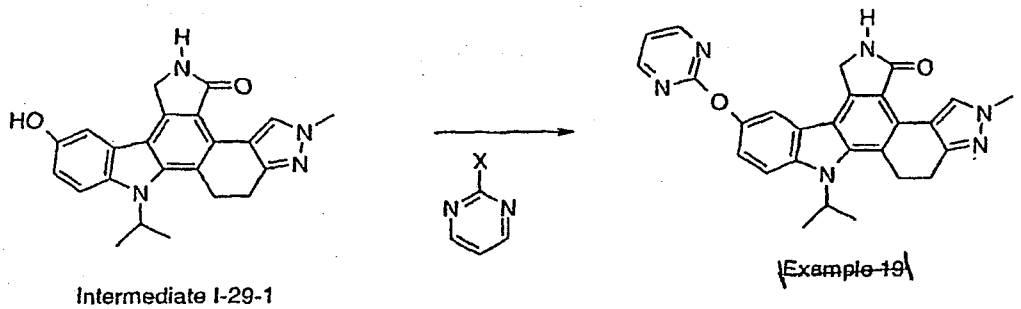


Intermediate I-14

Examples 1-2 ~~70-72~~

[0063] Scheme 1 outlines the route to prepare carbamate-type derivatives, such as Examples 1-2. An alternate method to preparing N, N-di-substituted carbamates utilized a nitrophenyl carbonate intermediate which may be treated with various primary or secondary amines. Similarly urea, O-carbamate, and N-carbamate derivatives may be prepared from reaction of the appropriate amine or phenol intermediate with an isocyanate or chloroformate or from the appropriate nitrophenyl carbonate, nitrophenyl carbamate, or trichloromethylcarbonyl (see J. Org. Chem. 2003, 68, 3733-3735).

Scheme 2



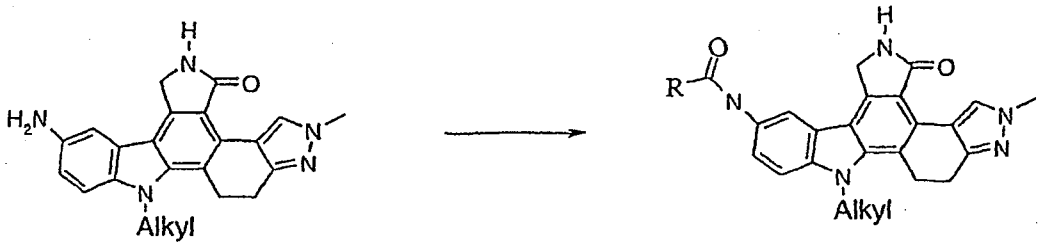
Intermediate I-29-1

~~Example 19~~

[0064] Scheme 2 outlines a route to prepare heteroaryl ethers from the corresponding phenol using a base such as sodium hydride and a heteroaryl bromide or chloride.

3

Scheme



Intermediate I-29

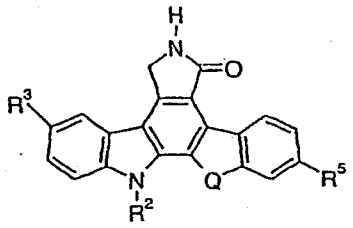
[0065] Scheme 3 shows a route for the preparation of N-carbamates or amides from the corresponding aniline intermediates I-29. Amino intermediates I-29 were prepared by alkylation of the appropriate cyano-esters with the appropriate alkyl iodide or bromide followed by nitration, and subsequent RaNi reduction to provide the amino-lactam. The desired compounds were readily prepared from the amine.

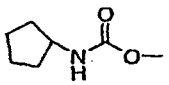
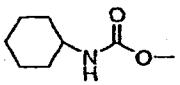
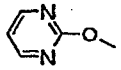
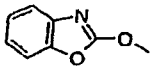
[0066] Heteroaryl ketones may be prepared using standard Friedel-Crafts type acylation reactions.

Examples

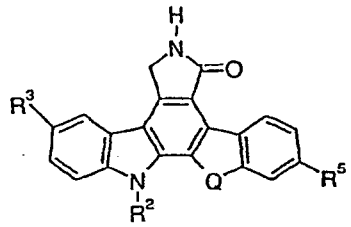
[0067] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments as shown in the following Tables 1-2. The compounds of Tables 1-2 show activity in the targets described herein at concentrations ranging from 0.1 nM to 10 μM. These examples are given for illustration of the invention and are not intended to be limiting thereof.

Table 1



Ex. No.	R^3	R^2	Q	R^5
1		H	CH_2CH_2	OiPr
2		H	CH_2CH_2	OiPr
3		H	CH_2CH_2	OiPr
4		H	CH_2CH_2	OiPr

(continued)



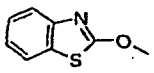
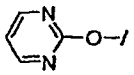
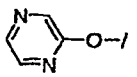
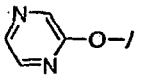
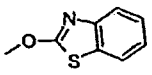
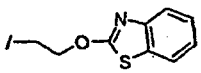
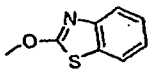
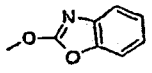
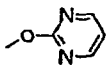
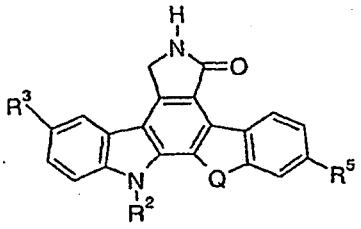
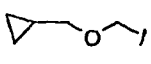
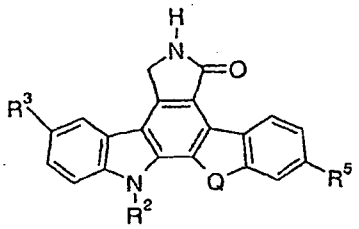
Ex. No.	R^3	R^2	Q	R^5
5		H	CH_2CH_2	OiPr
6		$CH_2CH_2CH_3$	CH_2CH_2	O^iPr
7		H	CH_2CH_2	O^iPr
8		$CH_2CH_2CH_3$	CH_2CH_2	O^iPr
9	H	CH_2CH_2OH	CH_2CH_2	
10	H		CH_2CH_2	
11	H	CH_2CH_2OH	CH_2CH_2	
12	H	H	CH_2CH_2	

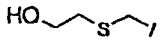
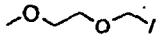
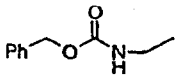
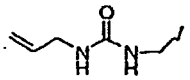
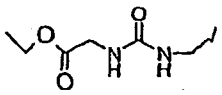
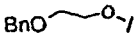
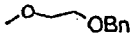
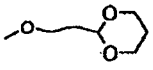
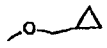
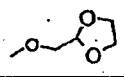
Table 2.



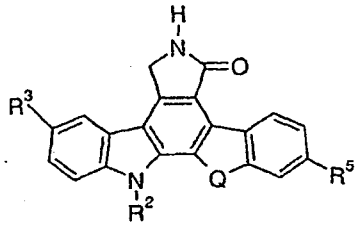
Eg.	R^3	R^2	Q	R^5
13		H	CH_2CH_2	OCH_3

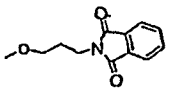
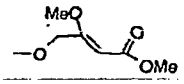
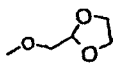
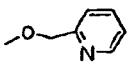
(continued)



Eg.	R^3	R^2	Q	R^5
14		CH_2CH_2OH	CH_2CH_2	OCH_3
15		CH_2CH_2OH	CH_2CH_2	OCH_3
16		H	CH_2CH_2	OiPr
17		CH_2CH_2OH	CH_2CH_2	OCH_3
18		H	CH_2CH_2	OCH_3
19		H	CH_2CH_2	OiPr
20		H	CH_2CH_2	OiPr
21		H	CH_2CH_2	OiPr
22	H	CH_2CH_2OH	CH_2CH_2	
23	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_2OH$
24	H	CH_2CH_2OH	CH_2CH_2	
25	H	CH_2CH_2OH	CH_2CH_2	$O[(CH_2)_2O]_2Me$
26	H	CH_2CH_2OH	CH_2CH_2	
27	H	CH_2CH_2OH	CH_2CH_2	
28	H	CH_2CH_2OH	CH_2CH_2	

(continued)



Eg.	R^3	R^2	Q	R^5
29	H	CH_2CH_2OH	CH_2CH_2	
30	H	CH_2CH_2OH	CH_2CH_2	$OCH(CH_3)CO_2Et$
31	H	CH_2CH_2OH	CH_2CH_2	
32	H	CH_2CH_2OH	CH_2CH_2	OCH_2CO_2tBu
33	H	H	CH_2CH_2	
34	H	CH_2CH_2OH	CH_2CH_2	OCH_2CO_2Et
35	H	CH_2CH_2OH	CH_2CH_2	
36	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_2OMe$
37	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_3CN$
38	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_5CN$
39	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_2OEt$
40	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_4CN$
41	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_6CN$
42	H	CH_2CH_2OH	CH_2CH_2	OCH_2CN
43	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_4C(=NH)O]Et$
44	H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_4CO_2H$
45	H	CH_2CH_2OH	CH_2CH_2	$O(CH2)_6CONH_2$

General procedure for Examples 1 and 2.

[0068] A mixture of phenol intermediate **I-14** (0.05 mmol.), isocyanate (0.05 mmol.), cesium hydrogen carbonate (0.5 mg) and tetrahydrofuran (0.5 mL) was stirred at room temperature for 1 day. The solvent was evaporated and the residue stirred for 8 hours with ethyl acetate and 3N HCl. The ethyl acetate was removed by evaporation and the aqueous solution was decanted from the solid. The residue was triturated with methanol and the product collected.

[0069] Example 1. (26%) MS m/e 510 (M+1); ^1H NMR (DMSO-d_6) δ 11.60 (s, 1H), 8.33 (s, 1H), 8.16 (d, 1H), 7.63 (d, 1H), 7.53 (s, 1H), 7.51 (d, 1H), 7.18 (d, 1H), 6.86 (s, 1H), 6.77 (d, 1H), 4.77 (s, 2H), 4.68 (m, 1H), 3.87 (m, 1H), 2.98 (t, 2H), 2.83 (t, 2H), 1.85 (m, 2H), 1.69 (m, 2H), 1.52 (m, 4H), 1.31 (d, 6H).

[0070] Example 2. (36%) MS m/e 524 (M+1); ^1H NMR (DMSO-d_6) 11.59 (s, 1H), 8.33 (s, 1H), 8.16 (d, 1H), 7.63 (s, 1H), 7.52 (d, 1H), 7.17 (d, 1H), 6.86 (s, 1H), 6.78 (d, 1H), 4.77 9s, 2H), 4.68 m, 1H), 3.00 (t, 2H), 2.83 (t, 2H), 1.87 (m,

2H), 1.72 (m, 2H), 1.56 (d, 1H), 1.30 (d, 6H).

[0071] Example 3. A suspension of sodium hydride (2.44 mg, 1.22 eq.) in 0.5 mL of THF was stirred under N_2 as phenol intermediate **I-14** (20.6 mg, 0.05 mmol) in 2.0 mL of THF:DMF (1:1) was added dropwise. After 10 minutes of stirring, 2-bromopyrimidine (8.9 mg, 1.12 equivalents) in 0.5 mL of THF was added. The mixture was stirred at 60 °C for 14 hours. The mixture was cooled to room temperature, diluted with CH_2Cl_2/MeOH, filtered through celite and concentrated. Purification was achieved by preparative TLC with CH_2Cl_2/MeOH (9:1) to afford the product (4.0 mg, 17%) (MS: 477 m/e $(M+M)^+$).

[0072] Example 4. The compound was prepared according to the procedure of Example 3 using phenol intermediate **I-14** and 2-chlorobenzoxazole; 40 hr; preparative TLC (10% MeOH in CH_2Cl_2); yield 28%; MS: 516 m/e $(M+1)^+$.

[0073] Example 5. The compound was prepared according to the procedure of Example 3 using intermediate I-14 and 2-chlorobenzothiazole; 40 hr; preparative TLC (10% MeOH in CH_2Cl_2); yield 13%; MS: 531 m/e $(M+1)^+$.

[0074] Example 6. To a mixture of Example 3 (25.0 mg, 0.052 mmol) and cesium carbonate (81 mg, 5.0 eq) in 2.0 mL of CH_3CN was added n-propyl bromide (47 ul, 10.0 eq.) under N_2. After stirring at 90 °C for 14 hours, the mixture was diluted with CH_2Cl_2, filtered through celite and concentrated. Purification by preparative TLC with 95% of CH_2Cl_2/ MeOH afforded the product (15.0 mg, 56%); MS: m/e 519 $(M+1)^+$.

[0075] Example 7. The compound was prepared using to the procedure of Example 3 using intermediate **I-14** and 2-bromopyrazine; preparative TLC (10% MeOH in CH_2Cl_2); MS 499 m/e $(M+1)^+$.

[0076] Example 8. The compound was prepared according to the procedure of Example 6 using Example 7 as starting material. MS m/e 519 (M + 1).

Synthesis of phenol intermediates **I-18** and **I-I9.**

[0077] A mixture of $AlCl_3$ (800 mg, 6 mmol) in dichloroethane (8 mL) was stirred at 0 °C as EtSH (1.40 mL) was added and followed by intermediate **I-41** (398 mg, 1 mmol). The reaction was stirred at 50 °C for 48 hr. To the reaction mixture was added 5 mL of 1N HCl and the mixture was stirred at rt for 0.5 hr. Filtration provided 240 mg (63%) of intermediate **I-18** (MS: 385 m/e $(M+1)^+$. By a similar method intermediate **I-19** was prepared from the methoxy N-H derivative.

[0078] Examples 9 and 10. A suspension of sodium hydride (12.2 mg, **I.22** eq.) in 0.5 mL of THF was stirred under N_2 as phenol intermediate **I-18** (76.8 mg, 0.2 mmol) in 4.0 mL of THF:DMF (1:1) was added dropwise at room temperature. After 10 minutes stirring, 2-chloro-benzothiazole (38 mg, 1.12 eq.) in 0.5 mL of THF was added. The mixture was then stirred at 60 °C for 40 hours, diluted with CH_2Cl_2/MeOH, filtered through celite and concentrated. Purification by preparative TLC with (9:1) CH_2Cl_2/MeOH afforded the mono product Example 9 (6.0 mg, yield 6%) (MS: 517 m/e $(M+H)^+$) and the dialkylated product Example 10 (60 mg, yield 46%) (MS: 651 m/e $(M+H)^+$).

[0079] Example 11. The compound was prepared according to the procedure of Example 10 using phenol intermediate **I-18** and 2-chlorobenzoxazole; 36 hr, preparative TLC (10% MeOH in CH_2Cl_2); yield 11%; MS: 502 m/e $(M+1)^+$.

[0080] Example 12. The compound was prepared according to the procedure of Example 10 using intermediate **I-19** and 2-bromopyrimidine; 36 hr; preparative TLC (10% MeOH in CH_2Cl_2); yield 25%; MS: 419 m/e $(M+1)^+$.

General procedure C for Examples 13 & 14:

[0081] To a well-stirred suspension of the CH_2OH intermediates I, II, or III in 7 mL of methylene chloride were added sequentially trifluoroacetic anhydride (5 equivalents) and N-methyl morpholine (5 eq) at 5 °C and under argon atmosphere. The resulted suspension was stirred at room temperature for 3 hours and the low boiling solvents were removed under vacuum. A stirred solution of this tritrifluoroacetate intermediate in an appropriate alcohol was heated to 80 °C for 6-48 hours in an oil bath. Gradually, the heterogeneous reaction mixture became homogeneous. When no starting material was observed by HPLC the reaction mixture was worked up by removing the solvent *in vacuo*. The residues was purified by either triturating with water or ether or alternatively, flash chromatography or preparative plate chromatography on silica gel using ethyl acetate or an ethyl acetate/hexane mixture.

[0082] Example 13. Pale yellow solid (31 mg, 54% yield). ^1H NMR (DMSO-d6, 300 MHz): & 0.05 (m, 2H). 0.49 (m, 2H), 1.06 (m, 1H), 2.79 (m, 2H), 3.82 (m, 5H). 4.65 (m, 4H), 4.79 (s, 2H), 4.97 (t, 1H), 6.80 (d, 1H), 6.89 (s, 1H), 7.46 (d, 1H), 7.65 (d, 1H), 7.87 (s, 1H), 7.89 (d, 1H), 8.36 (s, 1H); MS (ESI): m/e 483 $(M+1)^+$.

[0083] Example 14. Pale yellow solid (42.6 mg, 57% yield). ^1H NMR (DMSO-d6, 300 MHz): δ 2.55 (m, 2H), 2.80 (t, 2H), 3.86 (m, 4H), 3.98 (s, 2H), 4.61 (s, 1H), 4.73 (t, 1H), 4.80 (s, 2H), 4.98 (t, 1H), 6.78 (d, 1H), 6.89 (s, 1H), 7.50 (d, 1H), 7.68 (d, 1H), 7.88 (s, 1H), 7.90 (d, 1H), 8.38 (s, 1H): MS (ESI): m/e 489 $(M+1)^+$, 512 $(M+Na)^+$.

[0084] Example 15. To the tritrifluoroacetate (27mg) prepared using general method C was added 1 mL 2-methoxyethanol and the reaction was heated to 90°C in a sealed tube for 2 hours. The reaction was concentrated, the product triturated with ether, collected and dried. ^{1}HNMR(400MHz, DMSO) δ 8.38(1H, s), 7.89 (2H, d), 7.66 (1H, d), 7.47(1H, d), 6.90(1H, s), 6.81(1H, d), 4.98(2H,m), 4.79(1H, s), 4.67(3H, m), 3.96(6H, m), 3.82((2H, m), 3.62 (2H, m), 3.50(3H, m), 3.10(2H, m), 2.79(2H, m) MS m/e 487 $(M+1)^+$

[0085] Example 16. To the amino methyl intermediate XII CEP7668 (30 mg, 0.066 mmol) in THF (1 mL) was added TEA (9μl, 0.066 mmol), followed by benzyl chloroformate (9μl, 0.066 mmol) and the reaction mixture was stirred at room temperature overnight. Additional TEA and benzyl chloroformate were added while heating to 50°C. The reaction was concentrated, dissolved in ethyl acetated, washed with sodium bicarbonate, brine and dried over magnesium sulfate. The drying agent was removed by filtration and the solvent evaporated. The product was purified by preparative TLC using 2% methanol/methylene chloride. The product was collected and dried at 80°C overnight. MS m/e=590 $(m+1)^+$.

[0086] Example 17. This compound was prepared using the general procedure as Example 16 starting with 3-aminomethyl-N-ethanol intermediate XIII MS m/e 540 $(m+1)^+$.

[0087] Example 18. This compound was prepared from XII intermediate and ethyl isocyanato acetate. MS m/e 513 $(m+1)^+$.

[0088] Example 19. Phenol intermediate X CEP 7143 (15 mg, 0.037 mmol), bromoethylethylether (66 mg., 0.57 mmol) (added in 3 portions), acetone (7 mL) and 10N sodium hydroxide (4 mL.) were stirred at room temperature for 7 hr. The acetone was evaporated and the solution acidified to pH 3. The solid was collected, triturated with hexane and then extracted with methylene chloride. The extract was evaporated to give the product (0.004g.) (23%) MS m/e 471 (M+1); ^{1}H-NMR (DMSO-d_6) 11.40 (s, 1H), 8.33 (s, 1H). 8.16 (d, 1H),7.47 (d, 2H), 7.11 (d, 1H), 6.86 (s, 1H). 6.78 (d, 1H), 4.80 (s, 2H), 4.69 (m, 1H), 4.24 (m, 2H), 3.85 (m, 2H), 3.65 (t, 2H), 2.98 (t, 2H), 2.81 (t, 2H), 1.30 (d, 6H), 1.23 (t, 3H).

[0089] Example 20. A mixture of intermediate X (16.5 mg, 0.041 mmol) and cesium carbonate (88 mg, 1.1 eq) in 2.0 mL of CH_3CN was added cyclopentyl bromide (8.0 ul, 2.0 eq.) under N_2. After stirred at 70 °C for 24 hours, the mixture was diluted with CH_2Cl_2 and filtered through celite and concentrated. Purification by preparation TLC plate with CH_2Cl_2/MeOH afforded the product. MS m/e 533 (M+1).

[0090] Example 21. Prepared by hydrogenation of Example 1C in DMF using $Pd(OH)_2$ and a drop of HCl. MS m/e 443 (M+1)

[0091] Example 1C. A suspension of sodium hydride (2.44 mg, 1.22 eq.) in 0.5 mL of THF was stirred under N_2 as phenol intermediate X (3-hydroxy-10-isopropoxy-12,13-dihydro-6H,7H,14H-nephthyl(3,4-a)pyrrolo(3,3-a)pyrrolo(3,4-c) carbazole-7(7H)one) (20.6 mg, 0.05 mmol) in 2.0 mL of THF:DMF (1:1) was added dropwise. After 10 minutes of stirring, 2-bromopyrimidine (8.9 mg, 1.12eq.) in 0.5 mL of THF was added. The mixture was stirred at 60 °C for 14 hours. Then, the mixture was cooled to room temperature, diluted with CH_2Cl_2/MeOH, filtered through celite and concentrated. Purification was achieved by preparation TLC plate with CH_2Cl_2/MeOH (9:1) to afford the product (4.0 mg, 17%) (MS: 477 m/z $(M+H)^+$).

General Methods for Synthesis of Examples 22 - 45.

[0092] Method A: A mixture of hydroxyl intermediate (0.2 mmol), potassium iodide (3.3 mg, 0.1 eq.), N-tetrabutylammonium bromide (0.1 eq), cesium hydroxide hydrate (3 eq) and 20 mg of 4Å sieves in 2.0 mL of CH_3CN was added the appropriate alkyl bromide or iodide under N_2. After the mixture was stirred at 50 °C for 14-72 hours, the reaction mixture was diluted with CH_3CN and filtered through celite and concentrated. The residue was diluted with CH_2Cl_2 and washed with water and dried over magnesium sulfate. Purification by preparation TLC plate or crystallization with CH_2Cl_2/MeOH afforded the desired products.

[0093] Method B: A mixture of hydroxy intermediate (0.2 mmol) and cesium carbonate (3 eq) in 2.0 mL of CH_3CN was added the appropriate alkyl bromide or iodide under N_2. After the mixture was stirred at 50-80 °C for 14-72 hours, the reaction mixture was diluted with CH_3CN and filtered through celite and concentrated. The residue was diluted with CH_2Cl_2 and washed with water and dried over magnesium sulfate. Purification by preparation TLC plate or crystallization with CH_2Cl_2/MeOH afforded the desired product.

[0094] Method C: A mixture of hydroxyl intermediate (0.1 mmol), sodium hydroxide (1.5 eq.) and N-tetrabutylammonium bromide (0.1 eq) in 0.5 mL of CH_2Cl_2 and 0.5 mL of water was added the appropriate alkyl bromide under N_2. After the mixture was stirred at room temperature for 14-72 hours, the reaction mixture was concentrated and the residue was washed with water and dried over magnesium sulfate. Purification by preparation TLC plate with CH_2Cl_2/MeOH or crystallization afforded the desired product.

[0095] Example 22. A mixture of intermediate phenol XV (19.5 mg, 0.05 mmol), potassium carbonate (34.6 mg, 5 eq.) and potassium iodide (8.7 mg, 1.05 eq) in 1.5 mL of acetone and 0.25 mL of DMF was added the benzyl 2-bromoethyl ether (8.3 uL, 1.05 eq.) under N_2. After the mixture was stirred at reflux for 24 hours, the reaction mixture was diluted with EtOAc and washed with water, saturated NaCl solution and dried over magnesium sulfate. Purification by preparation TLC plate with 5% of MeOH/CH_2Cl_2 afforded the desired product (10 mg, 39%). MS m/e 519 m/z $(M+1)^+$.

[0096] Example 23. The product was obtained by first forming compound 23I by Method A, using phenol XV and cyclopentyl bromide; 14 hr; prep. TLC (10% MeOH in CH_2Cl_2); yield 10%; MS: m/e 453 m/z $(M+1)^+$. A mixture of compound 168I 110 (5 mg, 0.01 mmol), 10% $Pd(OH)_2$/C and 0.1 mL of conc. HCl in 1.0 mL of EtOH was hydrogenated under 42 psi H_2 on a Parr apparatus for 24 hours at room temperature. Filtration and concentration afforded 2.2 mg (27%) of the title compound. MS: m/e 451 m/z $(M+1)^+$.

[0097] Example 24. Method C from phenol XV and epibromohydrin; 22 hour, preparative TLC (10% MeOH in CH_2Cl_2): yield 30%; MS: m/e 463 m/z $(M+Na)^+$.

[0098] Example 25. Method C; phenol XV and 1-bromo-2-(2-methoxyethoxy)ethane, 14 hr; prep. TLC (10% MeOH in CH_2Cl_2); yield 11%; MS: 509 m/z $(M+Na)^+$.

[0099] Example 26. Method B; phenol XV and 2-(2-bromoethyl)-1,3-dioxane, 14 hr reflux; prep. TLC (10% MeOH in CH_2Cl_2); yield 54%; MS: 521 m/z $(M+1)^+$.

[0100] Example 27. Method A; phenol XV and (bromomethyl)cyclopropane, 14 hr; prep. TLC (10% MeOH in CH_2Cl_2); yield 17%; MS: m/e 439 m/z $(M+1)^+$.

[0101] Example 28. Method A; phenol XV and 2-bromomethyl-1,3-dioxolane; 64 hr; prep. TLC (10% MeOH in CH_2Cl_2); yield 15%; MS: 471 m/z $(M+1)^+$.

[0102] Example 29. Method B; phenol XV and N-(3-bromopropyl)phthalimide; 48 hr at 80 °C; prep. TLC (10% MeOH in CH_2Cl_2); yield 17%; MS: m/e 494 m/z $(M+Na)^+$.

[0103] Example 30. Method B; phenol XV and ethyl 2-bromopropionate; 14 hr at 80 °C; prep. TLC (10% MeOH in CH_2Cl_2); yield 9%; MS: m/e 507 m/z $(M+Na)^+$.

[0104] Example 31. Method A; phenol XV and methyl4-chloro-3-methoxy-(E)-2-butenoate; 40 hr at 80 °C; prep. TLC (10% MeOH in CH_2Cl_2); yield 21%; MS: m/e 535 m/z $(M+Na)^+$.

[0105] Example 32. Method A; phenol XV and 1-bromopinacolone; 14 hr at 60 °C; prep. TLC (10% MeOH in CH_2Cl_2); yield 29%; MS: m/e 505 m/z $(M+Na)^+$.

[0106] Example 33. Method A; 20 hr at 50 °C, prep. TLC (10% MeOH in CH_2Cl_2); yield (5%); MS: 449 m/z $(M+Na)^+$.

[0107] Example 34. Method B. (38%) MS m/e 471 (M+1); ^{1}H-NMR (DMSO-d_6) 8.37 (s, 1H), 7.90 (d, 1H), 7.83 (d, 1H), 7.64 (d, 1H), 7.46 (t, 1H), 7.25 (t, 1H), 6.86 (s, 1H), 6.75 (d 1H), 4.97 (t, 1H), 4.77 (d, 4H), 4.60 (t, 2H), 4.16 (m, 2H), 3.78 (m, 2H), 2.45 (s, 2H), 1.21 (t, 3H).

[0108] Example 35. Method B (19%) MS m/e 476 (M+1); ^{1}H-NNM (DMSO-d_6) 8.56 (s. 1H), 8:36 (s, 1H), 7.92 (d, 1H), 7.85 (m, 2H), 7.66 (d, 1H), 7.51 (d, 2H), 7.48 (t, 1H), 7.33 (m, 1H), 7.27 (t, 1H), 6.97 (s, 1H), 6.85 (d, 1H), 5.20 (s, 1H), 4.97 (m, 1H), 4.75 (s, 2H), 4.62 (m, 2H).

[0109] Example 36. Method B (43%) MS m/e 443 (M+1); ^{1}H-NMR (DMSO-d_6) 8.36 (s, 1H), 7.90 (d, 1h), 7.83 (d, 1H), 7.64 (d, 1H), 7.45 (t, 1H), 7.24 (t, 1H), 6.87 (s, 1H), 6.77 (d, 1H), 4.97 (t, 1H), 4.75 (s, 2H), 4.61 (s, 2H), 4.11 (s, 2H), 3.77 (d, 2H), 3.65 (s, 2H), 2.73 (s, 2H).

[0110] Example 37. Method B (63%) M S m/e 452 (M+1); ^{1}H-NMR (DMSO-d_6) 8.36 (s, 1H), 7.90 (d, 1H), 7.83 (d, 1H), 7.65 (d, 1H), 7.46 (t, 1H), 7.24 (t, 1H), 6.88 (s, 1H), 6.78 (d, 1H), 4.96 (t, 1H), 4.75 (s,2H), 4.60 (m, 2H), 4.07 (t, 2H), 3.78 (m, 2H), 2.74 (m, 2H), 2.64 (t, 2H), 2.02 (m, 2H).

[0111] Example 38. Method B (72%) M S m/e 480 (M+1); ^{1}H-NMR (DMSO-d_6) 8.35 (s, 1H), 7.91 (d, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 6.85 (t, 1H), 6.76 (t, 1H), 4.96 (t, 1H), 4.75 (s, 2H), 4.60 (s,2H), 4.00 (t,2H), 3.77 (d, 2H), 2.73 (m, 2H), 1.73 (t, 3H), 1.52 (m, 8H),

[0112] Example 39. Method B (67%) MS m/e 456 (M+1); ^{1}H-NMR (DMSO-d_6) 8.35 (s,1H), 7.91 (d,1H), 7.83 (d,1H), 7.64 (d,1H), 7.46 (t,1H), 7.24 (t,1H), 6.87 (s,1H), 6.75 (d,1H), 4.96 (t,1H), 4.75 (s,2H), 4.60 (t,2H),4.10 (s,2H), 3.78 (m, 2H), 3.70 (s,2H), 3.00 (m,2H), 2.70 (m,2H), 1.11 (T,3h).

[0113] Example 40. Method B (88%) M S m/e 466 (M+1); ^{1}H-NMR (DMSO-d_6) 8.35 (s, 1H), 7.91 (d, 1H), 7.83 (d, 1H), 7.64 (d, 1H), 7.46 (t, 1H), 7.24 (t, 1H), 6.86 (s. 1H), 6.77 (d, 1H), 4.96 (t, 1H), 4.75 (s, 2H), 4.61 (m, 2H), 4.03 (t, 2H), 3.78 (m, 2H), 2.74 (m, 2H), 2.54), (t, 2H), 1.73 (m, 6H).

[0114] Example 41. Method B. MS m/e 516 (M+1); ^{1}H-NMR (DMSO-d_6) 8.35 (s, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.64 (d, 1H), 7.46 (t, 1H), 7.24 (t, 1H), 6.85 (s, 1H), 6.76 (d, 1H), 4.96 (t, 1H), 4.75 (s, 2H), 4.60 (t, 2H), 3.99 (t, 2H), 3.78 (m, 2H), 2.74 (m, 2H), 1.71 (m. 2H), 1.56 (t, 4H), 1.42 (m, 6H).

[0115] Example 42. Method B. MS m/e 438 (M+1).

[0116] Example 43. This compound was formed from Example 40B, ethanol and gaseous hydrogen chloride (85%) MS m/e 512 (M+1); ^{1}H-NMR (DMSO-d_6) 8.35 (s, 1H), 7.91 (s, 1H), 7.83 (d, 1H), 7.65 (d, 1H),7.46 (t, 1H), 7.26 (t, 1H), 6.85 (s, 1H). 6.76 (d, 1H), 4.75 (s, 1H), 4.61 (m, 2H), 4.35 (m, 2H), 4.00 (m, 2H), 3.79 (m, 2H), 2.73 (m, 2H), 2.66 (m, 2H), 1.77 (m, 6H), 1.33 (t, 3H).

[0117] Example 44. Example 43 was refluxed in ethanol and concentrated hydrochloric acid for 18 hr. The solution was made basic with sodium hydroxide to pH 10 and refluxed 4 hours. The solution was acidified to precipitate the product. MS m/e 485 (M+1); ^{1}H-NMR (DMSO-d_6) 12.00 (s, 1H), 7.91 (d, 1H), 7.82 (d, 1H), 7.65 (d, 1H), 7.45 (t, 1H), 7.24 (m, 2H), 6.85 (s. 1H), 6.76 (d, 2H), 4.96 (t, 1H), 4. 75(s, 2H), 4.61 (m, 2H), 3.98 (t, 1H), 3.77 (m, 2H), 2.73(m, 2H), 2.23 (m, 4H), 1.71(m, 8H).

[0118] Example 45. The product was obtained from a reaction of Example 41 with ethanol and gaseous hydrogen chloride (45%) MS m/e 512 (M+1); ^{1}H-NMR (DMSO-d_6) 8.37 (s, 1H), 7.91 (d, 1H), 7.82 (d, 1H), 7.65 (d,1H), 7.47 (t, 1H), 7.23 (m, 2H), 6.86 (s, 1H), 6.77 (d, 2H), 6.67 (s, 1H), 4.99 (t, 1H), 4.76 (s, 2H), 4.61 (m, 2H), 3.98 (t, 1H), 3.80 (m, 2H), 2.74 (m, 2H), 2.02 (t, 2H), 1.71 (m, 2H), 1.38 (m, 8H).

[0119] Synthesis of intermediate phenol XVII CEP 5108: To aluminum trichloride (1.2 g, 9 mmol) in 12 mL anhydrous

dichloroethane was added 2 mL ethanethiol followed by methoxy derivative CEP 3371 (500 mg, 1.47 mmol). The mixture was stirred at 50°C for 48 h. The reaction was concentrated and stirred with 10 mL 1N hydrochloric acid for thirty minutes. The product was isolated by filtration and was dried in vacuo to afford 483 mg (quantitative) of a grey solid, the phenol. NMR (d_6-DMSO): 11.8 (s, 1H), 9.53 (s, 1H), 9.2 (d, 1H), 8.45 (s, 1H), 7.95 (s, 1H), 7.6 (d, 1H), 7.45 (dd, 1H), 7.25 (dd, 1H), 7.08 (s, 1H), 6.8 (dd, 1H), 4.85 (s, 2H), 4.08 (s, 2H). MS (ES +): 327 (M+1).

Utility

[0120] The compounds of the present invention are useful, inter alia, as therapeutic agents. Particularly, the compounds are useful for kinase inhibition, such as, for example, *trk*, VEGFR, PDGFR, PKC, MLK, DLK, Tie-2, FLT-3, and CDKI-6. Various compounds of the present invention show enhanced pharmaceutical properties over those disclosed in the art and improved pharmacokinetic properties in mammals. The compounds of the present invention show enhanced pharmaceutical properties over those disclosed in the art, including increased MLK and DLK dual inhibition activity, or increased VEGFR and Tie-2 dual inhibition activity, along with improved pharmacokinetic properties in mammals.

[0121] In one embodiment, the present invention provides compounds described herein for use in a method for treating or preventing diseases and disorders, such as those disclosed herein, which comprises administering to a subject in need of such treatment or prevention a therapeutically effective amount of a compound of the present invention.

[0122] In an additional embodiment, the present invention provides compounds described herein for use in a method for inhibiting *trk* kinase activity comprising providing a compound of the present invention in an amount sufficient to result in effective inhibition. Particularly, inhibition of *trk* implies utility in, for example, diseases of the prostate such as prostate cancer and benign prostate hyperplasia, as well as for the treatment of inflammation, such as neurological inflammation and chronic arthritis inflammation. In a preferred embodiment, the *trk* kinase receptor is *trk* A.

[0123] The majority of cancers have an absolute requirement for angiogenesis, the process by which new blood vessels are formed. The most potent angiogenic cytokine is vascular endothelial growth factor (VEGF) and there has been substantial research into the development of VEGF/VEGF receptor (VEGFR) antagonists. Receptor tyrosine kinase (RTK) inhibitors could have broad spectrum antitumor activity in patients with advanced pre-treated breast and colorectal carcinoma and Kaposi's sarcoma. Potentially these agents may play a role in the treatment of both early (adjuvant) and advanced cancer. The importance of angiogenesis for the progressive growth and viability of solid tumors is well established. Emerging data suggest an involvement of angiogenesis in the pathophysiology of hematologic malignancies as well. Recently, authors have reported increased angiogenesis in the bone marrow of patients with acute myeloid leukemia (AML) and normalization of bone marrow microvessel density when patients achieved a complete remission (CR) after induction chemotherapy. Tumor angiogenesis depends on the expression of specific mediators that initiate a cascade of events leading to the formation of new microvessels. Among these, VEGF (vascular endothelial growth factor), FGF (fibroblast growth factor) play a pivotal role in the induction of neovascularization in solid tumors. These cytokines stimulate migration and proliferation of endothelial cells and induce angiogenesis in vivo. Recent data suggest an important role for these mediators in hematologic malignancies as well. Isolated AML blasts overexpress VEGF and VEGF receptor 2. Thus, the VEGF/VEGFR-2 pathway can promote the growth of leukemic blasts in an autocrine and paracrine manner. Therefore, neovascularization and angiogenic mediators/receptors may be promising targets for anti-angiogenic and anti-leukemic treatment strategies. Thus, in other embodiments, the present invention provides compounds for use in a method for treating or preventing angiogenic disorders where VEGFR kinase activity contributes to pathological conditions, the method comprising providing a compound of the present invention in an amount sufficient to result in the vascular endothelial growth factor receptor being contacted with an effective inhibitory amount of the compound. Inhibition of VEGFR implies utility in, for example, angiogenic disorders such as cancer of solid tumors, endometriosis, macular degeneration, retinopathy, diabetic retinopathy, psoriasis, hemangioblastoma, as well as other ocular diseases and cancers.

[0124] FLT3, a member of the receptor tyrosine kinase (RTK) class III, is preferentially expressed on the surface of a high proportion of acute myeloid leukemia (AML) and B-lineage acute lymphocytic leukemia (ALL) cells in addition to hematopoietic stem cells, brain, placenta and liver. An interaction of FLT3 and its ligand has been shown to play an important role in the survival, proliferation and differentiation of not only normal hematopoetic cells but also leukemia cells. Mutations of the FLT3 gene was first reported as an internal tandem duplication (ITD) of the juxtamembrane (JM) domain-coding sequence, subsequently as a missense mutation of D835 within a kinase domain. ITD- and D835-mutations are essentially found in AML and their frequencies are approximately 20 and 6% of adults with AML, respectively. Thus, mutation of the FLT3 gene is so far the most frequent genetic alteration reported to be involved in AML. Several large-scale studies in well-documented patients published to date have demonstrated that ITD-mutation is strongly associated with leukocytosis and a poor prognosis. An inhibitor compound of FLT3 tyrosine kinase have an application in treatment of leukemia. The present invention provides compounds for use in a method for treating disorders characterized by responsiveness to FLT3 inhibition, the method comprising providing a compound of the present invention in an amount sufficient to result in the inhibition of FLT3.

[0125] Platelet-derived growth factor (PDGF) was one of the first polypeptide growth factors identified that signals through a cell surface tyrosine kinase receptor (PDGF-R) to stimulate various cellular functions including growth, proliferation, and differentiation. Since then, several related genes have been identified constituting a family of ligands (primarily PDGF A and B) and their cognate receptors (PDGF-R alpha and beta). To date, PDGF expression has been shown in a number of different solid tumors, from glioblastomas to prostate carcinomas. In these various tumor types, the biologic role of PDGF signaling can vary from autocrine stimulation of cancer cell growth to more subtle paracrine interactions involving adjacent stroma and even angiogenesis. Thus, in additional embodiments, the present invention provides compounds for use in a method for treating or preventing disorders where PDGFR activity contributes to pathological conditions, the method comprising providing a compound of the present invention in an amount sufficient to result in the platelet derived growth factor receptor being contacted with an effective inhibitory amount of the compound. Inhibition of PDGFR implies utility in, for example, various forms of neoplasia, rheumatoid arthritis, chronic arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, diseases with cardiovascular end points, such as atherosclerosis, restenosis, post-angioplasty restenosis, and the like.

[0126] In further embodiments, the present invention provides compounds for use in a method for treating or preventing disorders where MLK activity contributes to pathological conditions, such as those listed above, wherein the method comprises providing a compound of the present invention in an amount sufficient to result in the MLK receptor being contacted with an effective inhibitory amount of the compound. Inhibition of MLK implies utility in, for example, forms of cancer where MLKs play a pathological role as well as in neurological disorders.

[0127] In still other embodiments, the present invention provides compounds for use in a method for treating disorders characterized by the aberrant activity of trophic factor responsive cells, the method comprising providing a compound of the present invention in an amount sufficient to result in the trophic factor cell receptor being contacted with an effective activity inducing amount of the compound. In certain preferred embodiments, the activity of the trophic factor responsive cells is ChAT activity.

[0128] Fibroblast growth factor receptors (FGFR) are members of a family of polypeptides synthesized by a variety of cell types during the processes of embryonic development and in adult tissues. FGFR have been detected in normal and malignant cells and are involved in biological events that include mitogenic and angiogenic activity with a consequent crucial role in cell differentiation and development. To activate signal transduction pathways, FGFR are coupled to fibroblast growth factors (FGF) and heparan sulfate (HS) proteoglycans to form a biologically fundamental ternary complex. Based on these considerations, inhibitors able to block the signaling cascade through a direct interaction with FGFR could have antiangiogenesis and subsequent antitumor activity. Accordingly, the present invention provides compounds for use in a method for treating disorders characterized by the aberrant activity of FGF responsive cells, the method comprising providing a compound of the present invention in an amount sufficient to result in the FGFR being contacted with an effective activity inducing amount of the compound.

[0129] The compounds of the present invention can also have positive effects on the function and survival of trophic factor responsive cells by promoting the survival of neurons. With respect to the survival of a cholinergic neuron, for example, the compound may preserve the survival of a cholinergic neuronal population at risk of dying (due to, e.g., injury, a disease condition, a degenerative condition or natural progression) when compared to a cholinergic neuronal population not presented with such compound, if the treated population has a comparatively greater period of functionality than the non-treated population.

[0130] A variety of neurological disorders are characterized by neuronal cells which are dying, injured, functionally compromised, undergoing axonal degeneration, at risk of dying, etc. These neurodegenerative diseases and disorders include, but are not limited to, Alzheimer's disease; motor neuron disorders (e.g. amyotrophic lateral sclerosis); Parkinson's disease; cerebrovascular disorders (e.g., stroke, ischemia); Huntington's disease; AIDS dementia; epilepsy; multiple sclerosis; peripheral neuropathies including diabetic neuropathy and chemotherapy induced peripheral neuropathy, AID related peripheral neuropathy; disorders induced by excitatory amino acids; and disorders associated with concussive or penetrating injuries of the brain or spinal cord.

[0131] In other preferred embodiments, the compounds of the present invention are useful for treating or preventing multiple myeloma and leukemias including, but not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia.

[0132] In additional embodiments, the present compounds are also useful in the treatment of disorders associated with decreased ChAT activity or the death, injury to spinal cord motoneurons, and also have utility in, for example, diseases associated with apoptotic cell death of the central and peripheral nervous system, immune system and in inflammatory diseases. ChAT catalyzes the synthesis of the neurotransmitter acetylcholine, and it is considered an enzymatic marker for a functional cholinergic neuron. A functional neuron is also capable of survival. Neuron survival is assayed by quantification of the specific uptake and enzymatic conversion of a dye (e.g., calcein AM) by living neurons. The compounds described herein may also find utility in the treatment of disease states involving malignant cell proliferation, such as many cancers.

[0133] Additional embodiments of the invention are directed to any compound described herein, and stereoisomers

or pharmaceutically acceptable salts thereof, for use in the treatment and/or prevention of any of the conditions, diseases and disorders described above. Further embodiments are directed to the use of the compounds described herein, and stereoisomers or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating and/or preventing said conditions, disorders and diseases.

[0134] The compounds of the present invention have important functional pharmacological activities which find utility in a variety of settings, including both research and therapeutic arenas. For ease of presentation, and in order not to limit the range of utilities for which these compounds can be characterized, the activities of the compounds of the present invention can be generally described as follows:

A. Inhibition of enzymatic activity

B. Effect on the function and/or survival of trophic factor responsive cells

C. Inhibition of inflammation-associated responses

D. Inhibition of cell growth associated with hyperproliferative states

E. Inhibition of developmentally programmed motoneuron death

[0135] Inhibition of enzymatic activity can be determined using, for example, VEGFR inhibition (e.g., VEGFR2 inhibition), MLK inhibition (e.g., MLK1, MLK2 or MLK3 inhibition), PDGFR kinase inhibition, NGF-stimulated *trk* phosphorylation, PKC inhibition, or *trk* tyrosine kinase inhibition assays. Effect on the function and/or survival of trophic factor responsive cells, e.g., cells of a neuronal lineage, can be established using any of the following assays: (1) cultured spinal cord choline acetyltransferase ("ChAT") assay; (2) cultured dorsal root ganglion ("DRG") neurite extension assay; (3) cultured basal forebrain neuron ("BFN") ChAT activity assay. Inhibition of inflammation-associated response can be established using an indoleamine 2,3-dioxygenase ("IDO") mRNA assay. Inhibition of cell growth associated with hyperproliferative states can be determined by measuring the growth of cell lines of interest, such as an AT2 line in the case of prostate cancer. Inhibition of developmentally programmed motoneuron death can be assessed *in ovo* using embryonic chick somatic motoneurons, which cells undergo naturally occurring death between embryonic days 6 and 10, and analyzing inhibition of such naturally occurring cell death as mediated by the compounds disclosed herein.

[0136] The inhibition of enzymatic activity by the compounds of the present invention can be determined using, for example, the following assays:

VEGFR Inhibition Assay
MLK Inhibition Assay
PKC Activity Inhibition Assay
trkA Tyrosine Kinase Activity Inhibition Assay
Tie-2 Inhibition Assay
CDK1-6 Inhibition Assay
Inhibition of NGF-stimulated trk phosphorylation in a whole cell preparation
Platelet Derived Growth Factor Receptor (PDGFR) inhibition assay

[0137] A description of assays that may be used in connection with the present invention are set forth below. They are not intended, nor are they to be construed, as limiting the scope of the disclosure.

Inhibition of trkA Tyrosine Kinase Activity

[0138] Selected compounds of the present invention were tested for their ability to inhibit the kinase activity of baculovirus-expressed human trkA cytoplasmic domain using an ELISA-based assay as previously described (Angeles et al., Anal. Biochem. 236: 49-55, 1996). Briefly, the 96-well microtiter plate was coated with substrate solution (recombinant human phospholipase C-γl/glutathione S-transferase fusion protein (Rotin et al., EMBO J., 11: 559-567, 1992). Inhibition studies were performed in 100 μl assay mixtures containing 50 mM Hepes, pH 7.4,4μm ATP, 10 mM $MnCl_2$, 0.1% BSA, 2% DMSO, and various concentrations of inhibitor. The reaction was initiated by addition of trkA kinase and allowed to proceed for 15 minutes at 37°C. An antibody to phosphotyrosine (UBI) was then added, followed by a secondary enzyme-conjugated antibody, alkaline phosphatase-labelled goat anti-mouse IgG (Bio-Rad). The activity of the bound enzyme was measured via an amplified detection system (Gibco-BRL). Inhibition data were analyzed using the sigmoidal dose-response (variable slope) equation in GraphPad Prism. The concentration that resulted in 50% inhibition of kinase activity is referred to as "IC_{50}".

Inhibition of Vascular Endothelial Growth Factor Receptor Kinase Activity

[0139] Selected compounds of the present invention were examined for their inhibitory effects on the kinase activity of baculovirus-expressed VEGF receptor (human fik-1, KDR, VEGFR2) kinase domain using the procedure described for the trkA kinase ELISA assay described above. The kinase reaction mixture, consisting of 50 mM Hepes, pH 7.4, 40 μM ATP, 10 mM $MnCl_2$, 0.1% BSA, 2% DMSO, and various concentrations of inhibitor, was transferred to PLC-γ/GST-coated plates. VEGFR kinase was added and the reaction was allowed to proceed for 15 min. at 37°C. Detection of phosphorylated product was accomplished by addition of anti-phosphotyrosine antibody (UBI). A secondary enzyme-conjugated antibody was delivered to capture the antibody-phosphorylated PLC-γ/GST complex. The activity of the bound enzyme was measured via an amplified detection system (Gibco-BRL). Inhibition data were analyzed using the sigmoidal dose-response (variable slope) equation in GraphPad Prism.

Inhibition of Mixed Lineage Kinase-1 Activity

[0140] The kinase activity of MLK1 was assessed using the Millipore Multiscreen TCA "in-plate" format as described for protein kinase C (Pitt & Lee, J. Biomol. Screening, 1: 47-51, 1996). Briefly, each 50-μl assay mixture contained 20 mM Hepes, pH 7.0, 1 mM EGTA, 10 mM $MgCl_2$, 1 mM DTT, 25 mM (β-glycerophosphate, 60 μM ATP, 0.25 μCi [γ-^{32}P] ATP, 0.1% BSA, 500 μg/ml myelin basic protein (UBI #13-104), 2% DMSO, 1 μM of test compound, and 1 μg/ml of baculoviral GST-$MLK1_{KD}$. Samples were incubated for 15 min at 37°C. The reaction was stopped by adding ice cold 50% TCA and the proteins were allowed to precipitate for 30 min at 4°C. The plates were then washed with ice cold 25% TCA. Supermix scintillation cocktail was added, and the plates were allowed to equilibrate for 1-2 hours prior to counting using the Wallace MicroBeta 1450 PLUS scintillation counter.

Dual Leucine Zipper Bearing Kinase Assay

[0141] Compounds were tested for their ability to inhibit the kinase activity of recombinant baculoviral human DLK, containing the kinase domain and leucine zipper. Activity was measured in 384-well FluoroNunc plates (Cat#460372) using a time-resolved fluorescence readout (perkinElmer Application Note 1234-968). Plates were coated with 30 μl of the protein substrate MKK7 (Merritt et al. 1999) at a concentration of 20 μg/ml in Tris buffered saline (TBS). Each 30 μl assay contained 20 mM MOPS (pH 7.2), 15 mM $MgCl_2$, 0.1 mM Na_3VO_4, 1 mM DTT, 5 mM EGTA, 25 mM β-glycero-phosphate, 0.1% BSA, 100 μM ATP, and 2.5% DMSO. Reactions were started by the addition of 10 ng/ml GST-$hDLK_{KD/Lz}$. For IC_{50} determinations, a 10-point dose response curve was generated for each compound. Plates were incubated at 37°C for 30 minutes, and the reactions stopped by the addition of 100 mM EDTA. Product was detected using Europium-labeled anti-phosphothreonine (Wallac#AD0093; diluted 1:10000 in 3%BSA/T-TBS). Following over-night capture at 4°C, 50 μl enhancement solution (Wallac #1244-105) was added and the plate gently agitated for 5 min. The fluorescence of the resulting solution was then measured using the time-resolved fluorescence (TRF) mode in the Multilabel Reader (Victor2 Model # 1420-018 or Envision Model # 2100). Inhibition data was analyzed using GraphPad PRISM. See also Merritt, S.E., Mata, M., Nihalani, D., Zhu, C., Hu, X., and Holzman, L.B. (1999) The Mixed Lineage Kinase DLK utilizes MKK7 and not MKK4 as Substrate. J. Biol. Chem. 274, 10195-10202.

Tie-2 Tyrosine Kinase Assay

[0142] Compounds were tested for their ability to inhibit the kinase activity of recombinant baculoviral human His_6-Tie2 cytoplasmic domain using a modification of the ELISA described for trkA (Angeles *et al.*, 1996). A 384-well plate format was used for single-point screening while IC_{50}s were performed on 96-well plates. For single-point screening, each barcoded 384-well Costar High Binding plate (Cat # 3703) was coated with 50 μl/well of 10 μg/ml substrate solution (recombinant human GST- PLC-γ; Rotin et al.,1992) in Tris-buffered saline (TBS). The Tie2 activity was measured in 50-μl assay mixtures containing 50 mM HEPES (pH 7.2), 40 μM ATP, 10 mM $MnCl_2$, 2.5% DMSO, 0.05% BSA, and 200 ng/ml His_6-$Tie2_{CD}$. For IC_{50} determinations, the assays were run as described above but in 96-well Costar High Binding plates (Cat # 3703) and with the volumes doubled. A 10-point dose response curve was generated for each compound. The kinase reaction was allowed to proceed at 37°C for 20 minutes. The detection antibody, N1-Eu anti-phosphotyrosine (PT66) antibody (Wallac #AD0041), was added at 1:2000 diluted in block buffer [3% BSA in TBS with 0.05% Tween-20 (TBST)]. After one-hour incubation at 37°C, 50 μl of enhancement solution (Wallac #1244-105) was added and the plate was gently agitated. The fluorescence of the resulting solution was then measured using the time-resolved fluorescence (TRF) mode in the Multilabel Reader (Victor2 Model # 1420-018 or Envision Model # 2100). Inhibition data were analyzed using ActivityBase and IC_{50} curves were generated using XLFit. The cited references are as follows:

1. Angeles, T. S., Steffler, C., Bartlett, B. A., Hudkins, R. L., Stephens, R. M., Kaplan, D. R., and Dionne, C. A. (1996) Enzyme-linked immunosorbent assay for trkA tyrosine kinase activity. Anal. Biochem. 236, 49-55.
2. Rotin, D., Margolis, B., Mohammadi, M., Daly, RJ., Daum, G., Li, N., Fischer, E.H., Burgess, W.H., Ullrich, A., Schlessinger, J. (1992) SH2 domains prevent tyrosine dephosphorylation of the EGF receptor: identification of Tyr992 as the high-affinity binding site for SH2 domains of phospholipase C-γ. EMBO J. 11,559-567.

Dosage and Formulation

[0143] For therapeutic purposes, the compounds of the present invention can be administered by any means that results in the contact of the active agent with the agent's site of action in the body of the subject. The compounds may be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in combination with other therapeutic agents, such as, for example, analgesics. The compounds of the present invention are preferably administered in therapeutically effective amounts for the treatment of the diseases and disorders described herein to a subject in need thereof.

[0144] A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques. The effective dose will vary depending upon a number of factors, including the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, the formulation of the active agent with appropriate excipients, and the route of administration. Typically, the compounds are administered at lower dosage levels, with a gradual increase until the desired effect is achieved.

[0145] Typical dose ranges are from about 0.01 mg/kg to about 100 mg/kg of body weight per day, with a preferred dose from about 0.01 mg/kg to 10 mg/kg of body weight per day. A preferred daily dose for adult humans includes about 25, 50, 100 and 200 mg, and an equivalent dose in a human child. The compounds may be administered in one or more unit dose forms. The unit dose ranges from about 1 to about 500 mg administered one to four times a day, preferably from about 10 mg to about 300 mg, two times a day. In an alternate method of describing an effective dose, an oral unit dose is one that is necessary to achieve a blood serum level of about 0.05 to 20 μg/ml in a subject, and preferably about 1 to 20 μg/ml.

[0146] The compounds of the present invention may be formulated into pharmaceutical compositions by admixture with one or more pharmaceutically acceptable excipients. The excipients are selected on the basis of the chosen route of administration and standard pharmaceutical practice, as described, for example, in Remington: The Science and Practice of Pharmacy, 20th ed.; Gennaro, A. R., Ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2000. The compositions may be formulated to control and/or delay the release of the active agent(s), as in fast-dissolve, modified-release, or sustained-release formulations. Such controlled-release, or extended-release compositions may utilize, for example biocompatible, biodegradable lactide polymers, lactide/glycolide copolymers, polyoxyethylene-polyoxypropylene copolymers, or other solid or semisolid polymeric matrices known in the art.

[0147] The compositions can be prepared for administration by oral means; parenteral means, including intravenous, intramuscular, and subcutaneous routes; topical or transdermal means; transmucosal means, including rectal, vaginal, sublingual and buccal routes; ophthalmic means; or inhalation means. Preferably the compositions are prepared for oral administration, particularly in the form of tablets, capsules or syrups; for parenteral administration, particularly in the form of liquid solutions, suspensions or emulsions; for intranasal administration, particularly in the form of powders, nasal drops, or aerosols; or for topical administration, such as creams, ointments, solutions, suspensions aerosols, powders and the like.

[0148] For oral administration, the tablets, pills, powders, capsules, troches and the like can contain one or more of the following: diluents or fillers such as starch, or cellulose; binders such as microcrystalline cellulose, gelatins, or polyvinylpyrrolidones; disintegrants such as starch or cellulose derivatives; lubricants such as talc or magnesium stearate; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; or flavoring agents such as peppermint or cherry flavoring. Capsules may contain any of the afore listed excipients, and may additionally contain a semi-solid or liquid carrier, such as a polyethylene glycol. The solid oral dosage forms may have coatings of sugar, shellac, or enteric agents. Liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs, etc., or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as surfactants, suspending agents, emulsifying agents, diluents, sweetening and flavoring agents, dyes and preservatives.

[0149] The compositions may also be administered parenterally. The pharmaceutical forms acceptable for injectable use include, for example, sterile aqueous solutions, or suspensions. Aqueous carriers include mixtures of alcohols and water, buffered media, and the like. Nonaqueous solvents include alcohols and glycols, such as ethanol, and polyethylene glycols; oils, such as vegetable oils; fatty acids and fatty acid esters, and the like. Other components can be added including surfactants; such as hydroxypropylcellulose; isotonic agents, such as sodium chloride; fluid and nutrient replenishers; electrolyte replenishers; agents which control the release of the active compounds, such as aluminum mon-

ostearate, and various co-polymers; antibacterial agents, such as chlorobutanol, or phenol; buffers, and the like. The parenteral preparations can be enclosed in ampules, disposable syringes or multiple dose vials. Other potentially useful parenteral delivery systems for the active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes.

[0150] Other possible modes of administration include formulations for inhalation, which include such means as dry powder, aerosol, or drops. They may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for topical use are in the form of an ointment, cream, or gel. Typically these forms include a carrier, such as petrolatum, lanolin, stearyl alcohol, polyethylene glycols, or their combinations, and either an emulsifying agent, such as sodium lauryl sulfate, or a gelling agent, such as tragacanth. Formulations suitable for transdermal administration can be presented as discrete patches, as in a reservoir or microreservoir system, adhesive diffusion-controlled system or a matrix dispersion-type system. Formulations for buccal administration include, for example lozenges or pastilles and may also include a flavored base, such as sucrose or acacia, and other excipients such as glycocholate. Formulations suitable for rectal administration are preferably presented as unit-dose suppositories, with a solid based carrier, such as cocoa butter, and may include a salicylate.

[0151] As those skilled in the art will appreciate, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein, and the scope of the invention is intended to encompass all such variations.

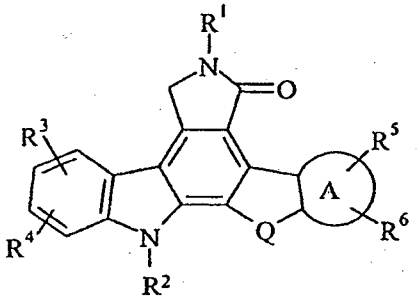
REFERENCES

[0152]

- WO02/092065
- WO02/17914
- WO00/47583
- US 5594009
- WO02/28874
- WO98/07433
- EP 0545195
- Gringrich et al., "J. Med. Chem.", 2003, 46(25), pages 5375-5388.
- Ruggeri et al. "Cancer Research", 2003, 63(18), pages 5978-5991.
- Sanchez-Martinez, et al., "Bioorganic & Medicinal Chemistry Letters", 2003, 13(21), pages 3835-3839.
- Lairol et al., "Expert Opinion on Investigational Drugs", 2003, 12(1), pages 51-64.

Claims

1. A fused pyrrolocarabazole compound of Formula II:



II

or a stereoisomer or a pharmaceutically acceptable salt thereof wherein:

ring A together with the carbon atoms to which it is attached, is a phenylene ring in which from 1 to 3 carbon atoms may be replaced by nitrogen atoms;

R^1 is H or optionally substituted alkyl, wherein said optional substituents are one to three R^{10} groups;
R^2 is selected from H, $C(=O)R^{2a}$, $C(=O)NR^{2C}R^{2d}$, SO_2R^{2b}, CO_2R^{2b}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{3-10} cycloalkyl and optionally substituted heterocycloalkyl, wherein said optional substituents are one to three R^{10} groups;
R^{2a} is selected from optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, OR^{2b}, $NR^{2c}R^{2d}$, $(CH_2)_pNR^{2c}R^{2d}$, and $O(CH_2)_pNR^{2c}R^{2d}$, wherein said optional substituents are one to three R^{10} groups;
R^{2b} is selected from H and optionally substituted C_{1-8} alkyl, wherein said optional substituents are one to three R^{10} groups;
R^{2c} and R^{2d} are each independently selected from H and optionally substituted C_{1-8} alkyl, or together with the nitrogen to which they are attached form an optionally substituted heterocycloalkyl, wherein said optional substituents are one to three R^{10} groups;

at least one of R^3, R^4, R^5, and R^6 is selected from the group consisting of OR^{14}; $C(=O)R^{22}$; $CH=NR^{26}$; $NR^{11}C(=O)R^{20}$; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$; $OC(=O)NR^{11}R^{20}$; $O\text{-}(C_{1-8}\text{alkylene})\text{-}R^{24}$; $Z^1\text{-}(C_{1-8}\text{alkylene})\text{-}R^{23}$, wherein Z^1 is selected from CO_2, O_2C, $C(=O)$, $NR^{11}C(=O)$, and $NR^{11}C(=O)O$; and $(C_{1-8}\text{ alkylene})\text{-}Z^2\text{-}(C_{1-8}\text{ alkylene})\text{-}R^{23}$, wherein Z^2 is selected from O, S(O)y, $C(=O)NR^{11}$, $NR^{11}C(=O)$, $NR^{11}C(=O)NR^{11}$, $OC(=O)NR^{11}$ and $NR^{11}C(=O)O$,
wherein said alkylene groups are optionally substituted with one to three R^{10} groups;
the other R^3, R^4, R^5, and R^6 moieties can be independently selected from the group consisting of H, R^{10}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl and optionally substituted C_{2-8} alkynyl, wherein said optional substitutents are one to three R^{10} groups;

Q is $-CH_2-CH_2-$;;

R^{10} is selected from C_{1-8} alkyl, C_{3-10} cycloalkyl, C_{3-10} spirocycloalkyl, C_{6-12} aryl, heteroaryl , heterocycloalkyl , C_{6-10} arylalkoxy, F, Cl, Br, I, CN, CF_3, $NR^{27A}R^{27B}$ NO_2, OR^{25} OCF_3, =O, $=NR^{25}$, $=N-OR^{25}$, $=N-N(R^{25})_2$, $OC(=O)NHR^{11}$, $O-Si(R^{16})_4$, O-tetrahydropyranyl, ethylene oxide, $NR^{16}C(=O)R^{25}$, $NR^{16}CO_2R^{25}$, $NR^{16}C(=O)NR^{27A}R^{27B}$, $NHC(=NH)NH_2$, $NR^{16}S(O)_2R^{25}$, $S(O)_yR^{25}$, CO_2R^{25}, $C(=O)NR^{27A}R^{27B}$, $C(=O)R^{25}$, CH_2OR^{25}, $(CH_2)_pOR^{25}$, $CH=NNR^{27A}R^{27B}$, $CH=NOR^{25}$, $CH=NR^{25}$, $CH=NNHCH(N=NH)NH_2$, $S(=O)_2NR^{27A}R^{27B}$, $P(=O)(OR^{25})_2$, OR^{13} and a monosaccharide wherein each hydroxyl group of the monosaccharide is independently either unsubstituted or is replaced by H, C_{1-8} alkyl, C_{1-8} alkylcarbonyloxy, or C_{1-8} alkoxy;

R^{11} is selected from H and optionally substituted C_{1-8} alkyl, wherein said optional substituents are one to three R^{10} groups;

R^{12} is selected from optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, and optionally substituted heteroaryl. , wherein said optional substituents are one to three R^{10} groups;

R^{13} is the residue of an amino acid after the removal of the hydroxyl moeity from the carboxyl group thereof;

R^{14} is a substituted heteroaryl, wherein said substituents is one to three R^{10} groups;

R^{15} is optionally substituted C_{1-8} alkyl, wherein said optional substituents is one to three R^{10} groups;

R^{16} is H or C_{1-8} alkyl;

R^{17} is selected from optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl,optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, wherein said optional substituents are one to three R^{10} groups;

R^{18} is selected from H, optionally substituted C_{1-8} alkyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl, optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, , wherein said optional substituents are one to three R^{10} groups;

R^{19} is selected from optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocycloalkyl, , and optionally substituted heteroaryl, , wherein said optional substituents are one to three R^{10} groups;

R^{20} is selected from substituted C_{6-12} aryl, substituted heteroaryl , optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, wherein said substituents are one to three R^{10} groups;

R^{21} is selected from substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, substituted C_{6-12} aryl, substituted arylalkyl, substituted heteroaryl , optionally substituted C_{3-10} cycloalkyl, and optionally substituted heterocycloalkyl, wherein said substituents are one to three R^{10} groups;

R^{22} is an substituted C_{6-12} aryl, substituted heteroaryl , wherein said substituents are one to three R^{10} groups;

R^{23} is selected from optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl, , optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocycloalkyl, , OR^{21}, $O(CH_2)_pOR^{21}$, $(CH_2)_pOR^{21}$, SR^{18}, SOR^{17}, SO_2R^{18}, CN, $N(R^{20})_2$, CHOH $(CH_2)_pN(R^{11})_2$, $C(=O)N(R^{18})_2$, $NR^{18}C(=O)R^{18}$, $NR^{18}C(=O)N(R^{18})_2$, $C(=NR^{18})OR^{18}$, $C(R^{12})=NOR^{18}$, $NHOR^{21}$, $NR^{18}C(=NR^{18})N(R^{18})_2$, NHCN, $CONR^{18}0R^{18}$, CO_2R^{18}, $OCOR^{17}$, $OC(=O)N(R^{18})_2$, $NR^{18}C(=O)OR^{17}$, and $C(=O)R^{18}$, wherein said optional substituents are one to three R^{10} groups;

R^{24} is selected from optionally substituted C_{2-8} alkenyl, optionally substituted C_{6-12} aryl, optionally substituted heteroaryl, , optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocycloalkyl, CN, OR^{21}, $O(CH_2)_pOR^{21}$, $(CH_2)_pOR^{21}$, SR^{19}, SOR^{17}, SO_2R^{18}, $CHOH(CH_2)_PN(R^{11})_2$, $NR^{18}C(=O)R^{18}$, $NR^{18}C(=O)N(R^{18})_2$, $C(=NR^{18})OR^{18}$, $NHOR^{21}$, $NR^{18}C(=NR^{18})N(R^{18})_2$, NHCN, $C(=O)N(R^{18})_2$, $C(=O)NR^{27A}R^{27B}$, $C(=O)NR^{11}R^{28}$, $C(=O)NR^{18}OR^{18}$, $C(=O)NR^{11}N(R^{11})_2$, $C(=O)NR^{11}$(alkylene)$NR^{27A}R^{27B}$, CO_2R^{18}, $OCOR^{17}$, $OC(=O)N(R^{18})_2$, $NR^{18}C(=O)OR^{17}$, $C(=O)NR^{11}R^{18}$ and $C(=O)R^{18}$, wherein said optional substituents are one to three R^{10} groups;

R^{25} is H, C_{1-8} alkyl, C_{6-12} aryl, heteroaryl, C_{3-10} cycloalkyl, or heterocycloalkyl;

R^{26} is selected from optionally substituted C_{3-10} cycloalkyl and optionally substituted heterocycloalkyl, , wherein said optional substituents are one to three R^{10} groups;

R^{27A} and R^{27B} are each independently selected from H and C_{1-8} alkyl, or together with the nitrogen to which they are attached form an optionally substituted heterocycloalkyl , wherein said optional substituents are selected from C_{1-8} alkyl, C_{6-12} aryl and heteroaryl;

R^{28} is optionally substituted arylalkyl, wherein said optional substituent is one to three R^{10} groups;

p is independently selected from 1, 2, 3, and 4; and

y is independently selected from 0, 1 and 2

wherein heterocycloalkyl refers to a saturated or partially saturated mono- or bicyclic alkyl ring system containing 3 to 10 carbon atoms in which one or more ring carbon atoms are replaced by at least one hetero atom such as -O-, -N-, or -S-;

and wherein heteroaryl refers to an aryl group containing 5 to 10 ring carbon atoms in which one or more carbon atoms are replaced by at least one hetero atom such as -O-, -N-, or -S-.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein R^2 is H, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, or optionally substituted cycloalkyl.

3. The compound of claim 2 or a pharmaceutically acceptable salt thereof wherein R^2 is H or optionally substituted alkyl.

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein at least one of R^3, R^4, R^5, and R^6 is OR^{14}; $C(=O)R^{22}$; $NR^{11}(=O)R^{20}$; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$; or $OC(=O)NR^{11}R^{20}$.

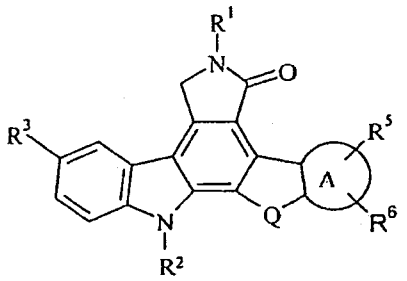
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein R^{14} is benzoxazolyl, benzothiazolyl, pyrimidyl, pyrazinyl or triazinyl; R^{22} is a 5-membered heteroaryl group; R^{20} is heterocycloalkyl or heteroaryl; R^{23} is heteroaryl, or heterocycloalkyl; R^{24} is heteroaryl; and R^{26} is heterocycloalkyl, wherein each of said R^{14}, R^{22}, R^{20}, R^{23}, R^{24} and R^{16} moieties is optionally substituted with 1 to 3 R^{10} groups.

6. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein R^2 is H, $C(=O)R^{2a}$, $C(=O)NR^{2c}R^{2d}$, SO_2R^{2b}, CO_2R^{2b}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, or optionally substituted C_{3-10} cycloalkyl.

7. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein R^1 is H or C_{1-8} alkyl.

8. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein at least one of R^3, R^4, R^5, and R^6 is OR^{14}, wherein R^{14} is benzoxazole, benzothiazole, pyrimidine, pyrazine or triazine; $C(=O)R^{22}$, wherein R^{22} is a 5-membered heteroaryl group; $NR^{11}C(=O)R^{20}$, wherein R^{20} is heteroaryl; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$, wherein R^{20} is heterocycloalkyl; or $OC(=O)NR^{11}R^{20}$, wherein R^{20} is cycloalkyl, wherein each of said R^{14}, R^{22}, and R^{20} moieties is optionally substituted with 1 to 3 R^{10} groups.

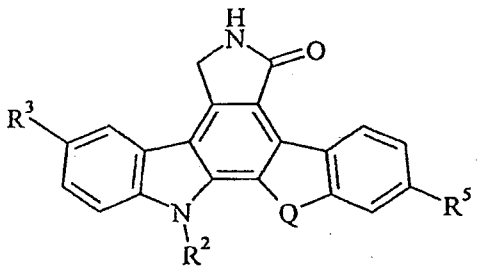
9. The compound of claim 1 or a pharmaceutically acceptable salt thereof having a structure of Formula III:



III

wherein R^1 is H or alkyl.

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof having a structure of Formula IV:



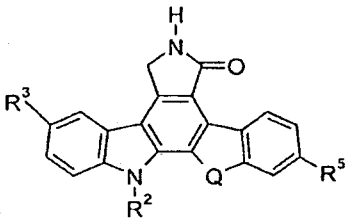
IV

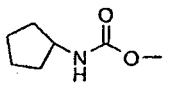
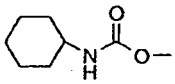
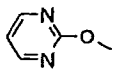
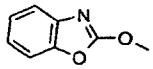
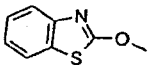
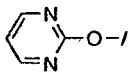
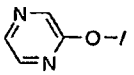
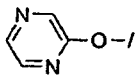
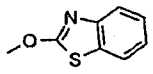
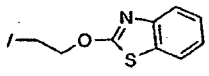
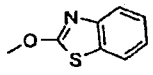
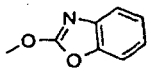
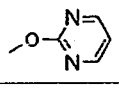
11. The compound of claims 9 or 10 or a pharmaceutically acceptable salt thereof wherein R^2 is H, $C(=O)R^{2a}$, $C(=O)NR^{2c}R^{2d}$, SO_2R^{2b}, CO_2R^{2b}, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, or optionally substituted C_{3-10} cycloalkyl.

12. The compound of claim 11 or a pharmaceutically acceptable salt thereof wherein R^2 is H or optionally substituted C_{1-8} alkyl.

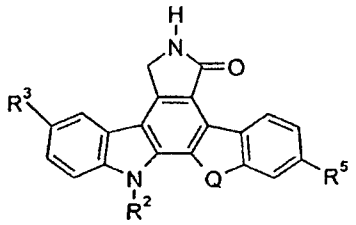
13. The compound of claims 9, 10, or 11 or a pharmaceutically acceptable salt thereof wherein at least one of R^3, R^4, R^5, and R^6 is OR^{14}, wherein R^{14} is benzoxazole, benzothiazole, pyrimidine, pyrazine or triazine; $C(=O)R^{22}$, wherein R^{22} is a 5-membered heteroaryl; $NR^{11}C(=O)R^{20}$, wherein R^{20} is heteroaryl; $NR^{11}C(=O)OR^{15}$; $OC(=O)R^{20}$, wherein R^{20} is heterocycloalkyl; or $OC(=O)NR^{11}R^{20}$, wherein R^{20} is cycloalkyl, wherein each of said R^{14}, R^{22}, and R^{20} moieties is optionally substituted with 1 to 3 R^{10} groups.

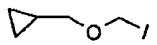
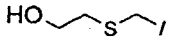
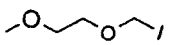
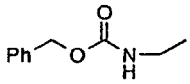
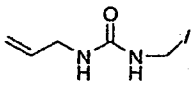
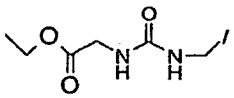
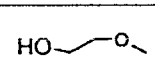
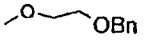
14. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein the compounds are selected in accordance with the following table:



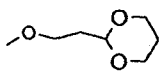
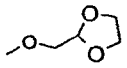
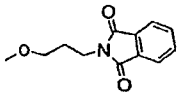
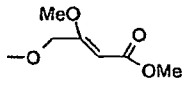
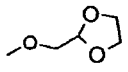
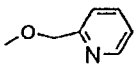
R^3	R^2	Q	R^5
	H	CH_2CH_2	OiPr
	H	CH_2CH_2	OiPr
	H	CH_2CH_2	OiPr
	H	CH_2CH_2	OiPr
	H	CH_2CH_2	OiPr
	$CH_2CH_2CH_3$	CH_2CH_2	O^iPr
	H	CH_2CH_2	O^iPr
	$CH_2CH_2CH_3$	CH_2CH_2	O^iPr
H	CH_2CH_2OH	CH_2CH_2	
H		CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	
H	H	CH_2CH_2	

15. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein the compounds are selected in accordance with the following table:



R^3	R^2	Q	R^5
	H	CH_2CH_2	OCH_3
	CH_2CH_2OH	CH_2CH_2	OCH_3
	CH_2CH_2OH	CH_2CH_2	OCH_3
	H	CH_2CH_2	OiPr
	CH_2CH_2OH	CH_2CH_2	OCH_3
	H	CH_2CH_2	OCH_3
	H	CH_2CH_2	OiPr
	H	CH_2CH_2	OiPr
	H	CH_2CH_2	OiPr
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_2OH$
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	$O[(CH_2)_2O]_2Me$

(continued)

R^3	R^2	Q	R^5
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	$OCH(CH_3)CO_2Et$
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	OCH_2CO_2tBu
H	H	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	OCH_2CO_2Et
H	CH_2CH_2OH	CH_2CH_2	
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_2OMe$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_3CN$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_5CN$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_2OEt$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_4CN$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_6CN$
H	CH_2CH_2OH	CH_2CH_2	OCH_2CN
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_4C(=NH)OEt$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_4CO_2H$
H	CH_2CH_2OH	CH_2CH_2	$O(CH_2)_6CONH_2$

(continued)

R^3	R^2	Q	R^5

16. A pharmaceutical composition comprising a compound of claim 1 or a stereoisomer or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

17. The compound of any of claims 1-15 or a pharmaceutically acceptable salt thereof for use in therapy.

18. The use of a compound of any of claims 1-15 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating an angiogenic disorder.

19. A compound of any of claims 1-15 or a pharmaceutically acceptable salt thereof for use in a method of treating an angiogenic disorder

20. The use of claim 18 or the compound or salt as claimed in claim 19 wherein the angiogenic disorder is selected from: cancer of solid tumors, hematologic tumors, macular degeneration, retinopathy, diabetic retinopathy, psoriasis, endometriosis, and hemangioblastoma.

21. The use of a compound of any of claims 1-15 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating multiple myeloma or leukemia.

22. A compound of any of claims 1-15 or a pharmaceutically acceptable salt thereof for use in a method of treating multiple myeloma or leukemia.

23. The use of claim 20 or the compound as claimed in claim 22 wherein the leukemia is acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, or chronic lymphocytic leukemia.