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(54) Title: PROCESSES FOR PRODUCING 4-AMINOQUINAZOLINES

(57) Abstract: The present invention relates to methods for preparing compounds of formula (I): or suitable salts thereof useful as inhibitors of voltage-gated sodium channels and calcium channels. The invention also relates to methods for preparing intermediates related thereto.

VPI/04-143 WO

PROCESSES FOR PRODUCING 4-AMINOQUINAZOLINES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit, under 35 U.S.C. §119, of United States Provisional Application number: 60/637,278 filed December 17, 2004, entitled "Processes for Producing 4-Aminoquinazolines" and the entire contents of this application are hereby incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

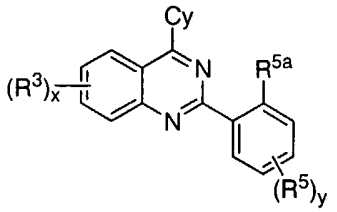
[0002] The present invention relates to methods of preparing compounds useful as inhibitors of ion channels, and intermediates thereto.

BACKGROUND OF THE INVENTION

[0003] The present invention provides processes for producing 4-amino-quinazolines and analogs thereof. These compounds are useful as inhibitors of voltage-gated sodium channels and calcium channels.

SUMMARY OF THE INVENTION

[0004] As described herein, the present invention provides methods for preparing compounds useful as inhibitors of voltage-gated sodium channels and calcium channels. Such compounds include compounds of formula **I**:



I

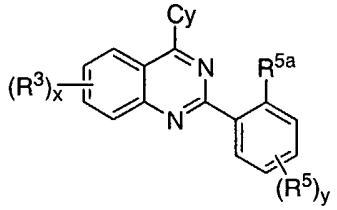
or suitable salts thereof;

wherein Cy, R^3, x, R^{5a}, R^5 and y are as defined in any of the embodiments herein.

[0005] The present invention also provides compounds useful as intermediates in the processes of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0006] The compounds of the present invention include compounds of formula **I**:

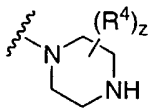


I

or suitable salts thereof;

wherein:

Cy is a ring selected from:



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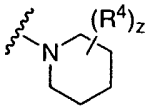

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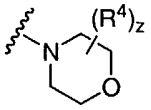

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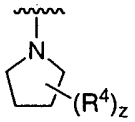

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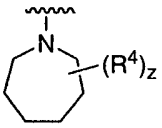

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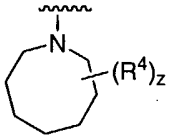

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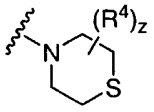

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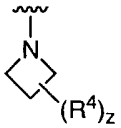

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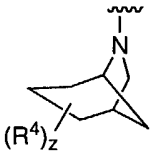

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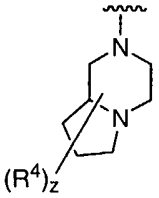

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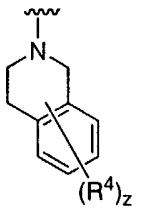

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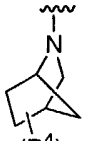


oo

wherein Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

R^{5a} is Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0007] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0008] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0009] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the

molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0010] The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

[0011] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0012] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0013] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0014] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0015] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0016] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0017] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0018] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are generally selected from halogen; -R°; -OR°; -SR°; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; -CH=CH(Ph), optionally substituted with R°; $-NO_2$; -CN; $-N(R^{\circ})_2$; $-NR^{\circ}C(O)R^{\circ}$; $-NR^{\circ}C(S)R^{\circ}$; $-NR^{\circ}C(O)N(R^{\circ})_2$; $-NR^{\circ}C(S)N(R^{\circ})_2$; $-NR^{\circ}CO_2R^{\circ}$; $-NR^{\circ}NR^{\circ}C(O)R^{\circ}$; $-NR^{\circ}NR^{\circ}C(O)N(R^{\circ})_2$; $-NR^{\circ}NR^{\circ}CO_2R^{\circ}$; $-C(O)C(O)R^{\circ}$; $-C(O)CH_2C(O)R^{\circ}$; $-CO_2R^{\circ}$; $-C(O)R^{\circ}$; $-C(S)R^{\circ}$; $-C(O)N(R^{\circ})_2$; $-C(S)N(R^{\circ})_2$; $-OC(O)N(R^{\circ})_2$; $-OC(O)R^{\circ}$; $-C(O)N(OR^{\circ})\ R^{\circ}$; $-C(NOR^{\circ})\ R^{\circ}$; $-S(O)_2R^{\circ}$; $-S(O)_3R^{\circ}$; $-SO_2N(R^{\circ})_2$; $-S(O)R^{\circ}$; $-NR^{\circ}SO_2N(R^{\circ})_2$; $-NR^{\circ}SO_2R^{\circ}$; $-N(OR^{\circ})R^{\circ}$; $-C(=NH)-N(R^{\circ})_2$; $-P(O)_2R^{\circ}$; $-PO(R^{\circ})_2$; $-OPO(R^{\circ})_2$; $-(CH_2)_{0-2}NHC(O)R^{\circ}$; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; or -CH=CH(Ph), optionally substituted with R°; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2(Ph)$, or, notwithstanding the definition above, two independent occurrences of R°, on the same substituent or different substituents, taken together with the atom(s) to which each R° group

is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0019] Optional substituents on the aliphatic group of R° are selected from NH_2, $NH(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}$aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$aliphatic), $O(haloC_{1-4}$ aliphatic), or $haloC_{1-4}$aliphatic, wherein each of the foregoing C_{1-4}aliphatic groups of R° is unsubstituted.

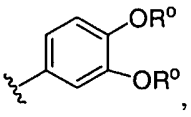
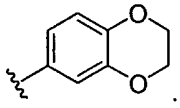
[0020] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$(alkyl), $=NNHSO_2$(alkyl), or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

[0021] Unless otherwise defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^{+1})_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2$(Ph), optionally substituted $-(CH_2)_{1-2}$(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0022] Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, -OH, $-O(C_{1-4}$ aliphatic), $-NO_2$, -CN, $-CO_2H$, $-CO_2(C_{1-4}$ aliphatic), -O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^+ is unsubstituted.

[0023] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

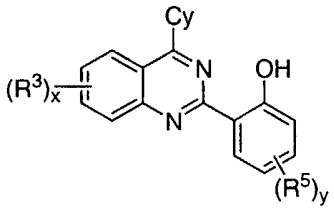
[0024] As detailed above, in some embodiments, two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0025] Exemplary rings that are formed when two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^o)_2$, where both occurrences of R^o are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^o  , these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:  . It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[0026] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein

are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0027] In certain embodiments, the methods described herein are useful for preparing compounds of formula **Ia**:

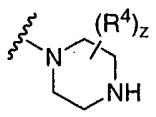


Ia

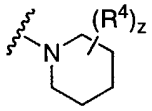
or suitable salts thereof;

wherein:

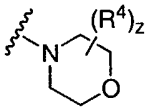
Cy is a ring selected from:



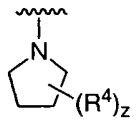
cc



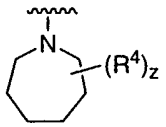
dd



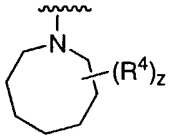
ee



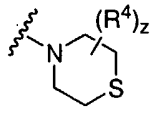
ff



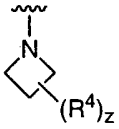
gg



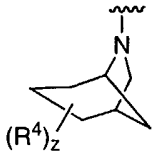
hh



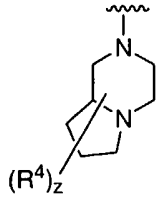
ii



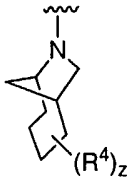
jj



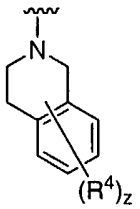
kk



ll



mm



nn

oo

wherein Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

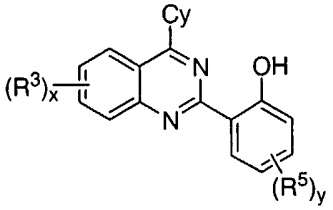
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0028] In other embodiments, the methods described herein are useful for preparing compounds of formula **Ia**:



Ia

or suitable salts thereof;

wherein:

Cy is azetidin-1-yl (**jj**), pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), or piperazin-1-yl (**cc**), wherein Cy is optionally substituted with 0-4 occurences of R^4;

each R^4 is independently Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-C(O)CH(OH)CH_2CH(CH_3)_2$, $-C(O)CH(OH)CH_2C(CH_3)_3$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, $-CH_2$cyclohexyl, pyridyl, $-CH_2$pyridyl, or $-CH_2$thiazolyl;

x is 1 or 2;

each occurrence of R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy;

y is 0-4; and

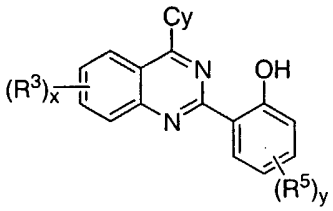
each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0029] In still other embodiments, the methods described herein are useful for preparing compounds of formula **Ia** wherein x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN. In yet other embodiments, x is 1

and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. In certain other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is methyl.

[0030] According to another embodiment, Cy is piperazin-1-yl (**cc**), y is 0, x is 1 and R^3 is at the 7-position of the quinazoline ring and is methyl.

[0031] According to yet another embodiment, the methods described herein are useful for preparing compounds of formula **Ia**:



Ia

or suitable salts thereof;

wherein:

Cy is an optionally substituted ring selected from azetidin-1-yl (**jj**), pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), or piperazin-1-yl (**cc**), wherein Cy is optionally substituted with 0-4 occurences of R^4;

each R^4 is independently Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-C(O)CH(OH)CH_2CH(CH_3)_2$, $-C(O)CH(OH)CH_2C(CH_3)_3$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, $-CH_2$cyclohexyl, pyridyl, $-CH_2$pyridyl, or $-CH_2$thiazolyl;

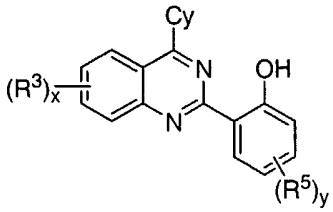
x is 1;

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$;

y is 0 or 1; and

each R^5 is independently Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

[0032] In certain embodiments, the methods described herein are useful for preparing compounds of formula **Ia**:



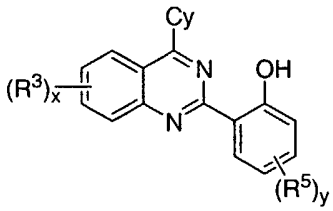
Ia

or suitable salts thereof;

wherein:

Cy is unsubstituted piperazin-1-yl, x is 1 and y is 0.

[0033] In certain other embodiments, the methods described herein are useful for preparing compounds of formula **Ia**:



Ia

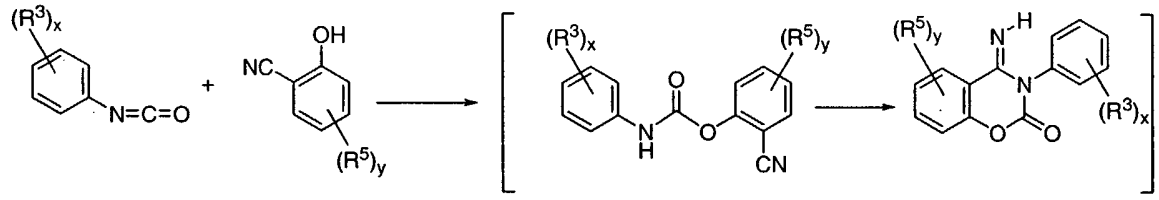
or suitable salts thereof;

wherein:

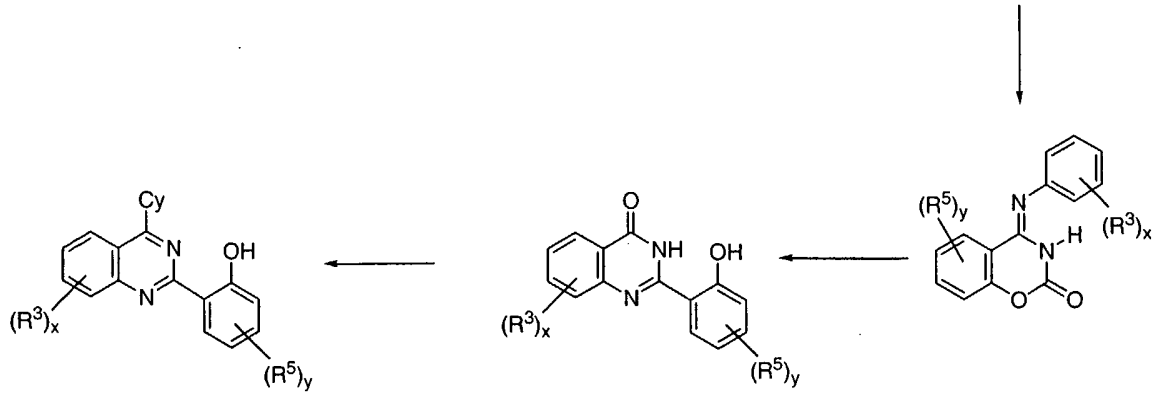
Cy is piperazin-1-yl optionally substituted on the nitrogen with R^4, x is 1 and y is 0.

[0034] Compounds of formula **Ia** are prepared generally as depicted in Scheme I, below.

Scheme I



1 **2** **3** **4**



Ia **6** **5**

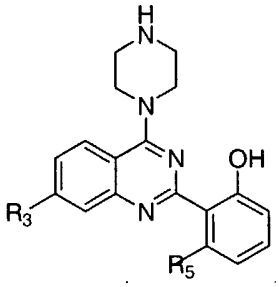
[0035] Scheme I above depicts a general method for preparing compounds of formula **Ia**. As is readily apparent, such compounds of formula **Ia** correspond to compounds of formula **I** wherein R^{5a} is –OH. One of ordinary skill in the art would recognize that a variety of compounds of formula **I**, wherein R^{5a} is other than –OH are prepared from intermediate **6** or a suitable salt thereof using methods known in the art. For example, the –OH group of intermediate **6** may be converted to a suitable leaving group. As used herein, a suitable leaving group is a chemical moiety that is readily displaced by a desired incoming chemical moiety. Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 4th Ed., pp. 351-357, John Wiley and Sons, N.Y. (1992) and "Comprehensive Organic Transformations," Larock, Richard C., 2nd Ed., John Wiley & Sons, 1999, the contents both of which are incorporated herein by reference.

[0036] Such leaving groups include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyl, optionally substituted alkenylsulfonyl, optionally substituted arylsulfonyl, and diazonium moieties.

[0037] The suitable leaving group may then be displaced by a variety of moieties to form compounds of formula **I**. Thus, it will be appreciated that after the hydroxyl group of intermediate **6** is converted to a suitable leaving group, a variety of functional groups may be incorporated to form a compound of formula **I** having a variety of R^{5a} groups. For example, said leaving group by be displaced by halogen, a haloalkyl moiety, an alkyl moiety, CN, a carboxylate moiety, NH_3, $NH(CH_3)_2$, $N(Et)_2$, $NH(iPr)_2$, $HO(CH_2)_2OCH_3$, $HCONH_2$, $HCOOCH_3$, $HOCH_3$, $HOCH_2CH_3$, HCH_2OH, NH_2COCH_3, HSO_2NH_2, $HSO_2NHC(CH_3)_2$, $HOCOC(CH_3)_3$, $HOCOCH_2C(CH_3)_3$, $HO(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $HOCOCH(CH_3)_2$, HOCO(cyclopentyl), $HCOCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy to form a compound of formula **I**. One of ordinary skill in

the art would also recognize that these groups may be activated in order to affect said displacement.

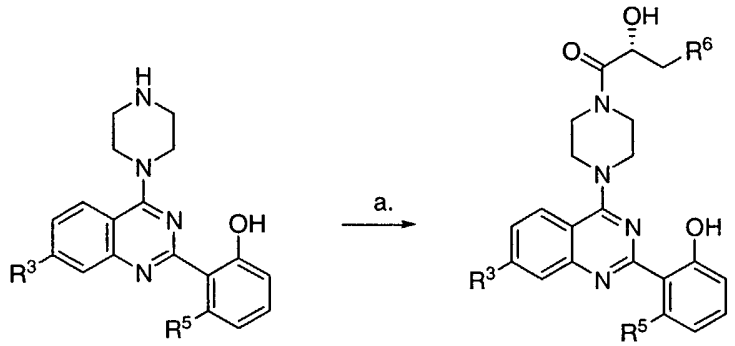
[0038] According to another embodiment of the present invention, the methods described herein are useful for preparing compound **Iaa-1** or a suitable salt thereof:



Iaa-1

wherein R^3 is methyl or hydrogen and R^5 is fluorine or hydrogen.

[0039] According to another embodiment of the present invention, the methods described herein are useful for preparing a compound of formula **V** from a compound of formula **Iaa-1**:



Iaa-1 **V**

comprising the additional step of:

(a) reacting a compound of formula **Iaa-1** with with a suitable acid under suitable amide coupling conditions;

wherein R^6 is isopropyl or t-butyl, R^3 is methyl or hydrogen, and R^5 is fluorine or hydrogen.

[0040] In one embodiment of compounds of formula **V**, R^6 is isopropyl, R^3 is methyl, and R^5 is hydrogen. In another embodiment of formula **V**, R^6 is t-butyl, R^3 is methyl, and R^5 is hydrogen. In yet another embodiment of formula **V**, R^6 is isopropyl, R^3 is hydrogen, and R^5 is hydrogen. In yet another embodiment of formula **V**, R^6 is t-butyl, R^3 is methyl, and R^5 is fluorine. Or, in formula **V**, R^6 is t-butyl, R^3 is hydrogen, and R^5 is fluorine.

[0041] In one embodiment, suitable amide coupling conditions include a variety of commonly used organic solvents (such as methylene chloride, THE, ethyl acetate, acetonitrile, DMF, etc.), commercially available amide coupling reagents known to those skilled in the art (such as EDC, BOP, BOP-Cl, DCC, HOBt, etc.), inorganic (such as K_2CO_3, Na_2CO_3, Cs_2CO_3) or organic bases (Et_3N, Hunigs base, N-methylmorpholine, imidazole, 4-DMAP,etc.) and a suitable reaction temperature (from 0°C to greater than 100°C) and a suitable atmosphere (such as air, nitrogen , argon, etc.). In one embodiment for preparing compounds of formula V, the organic solvent in DMF, the the coupling agents are EDC and HOBt, the organic base is 4-methylmorpholine, the atmosphere is nitrogen adn the temperature is room temperature.

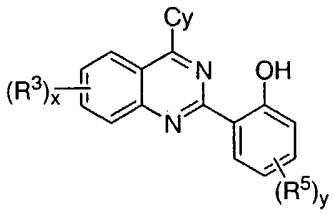
[0042] In another embodiment, the method further comprises the step of forming a salt of the compound of formula **V**. In one embodiment the salt is a methanesulfonic acid salt.

[0043] One of ordinary skill in the art would recognize that compounds of formula **V** may be prepared using methods known in the art. For instance, for preparing compound **V**, wherein R^6 is isopropyl or t-butyl, the commercially available or synthesized acid intermediate coupling partner is used along with the suitable amide coupling reagents either with or without added organic or inorganinc base and in a variety of commonly used organic solvents. In one embodiment, wherein R^6 is isopropyl, one of skill in the art would be able to make the coupling partner isocaproic acid from leucine by known organic chemistry techniques. Finally, one of skill in the art would recognize that the free base of compounds of formula **V** may be converted to a suitable salt for further purification. In one embodiment, the methanesulfonic acid salt is useful for purifying compounds of formula **V**.

[0044] In another embodiment, the compound of formula **Ia** is produced as a salt of a sulfonic acid or a dicarboxylic acid. The specific sulfonic acid or dicarboxylic acid useful for producing the salt of compound of formula **Ia** may be selected from acids known in the art. See, e.g., "Practical Process, Research, & Development," Anderson, Neal G., Academic Press, 2000, the contents of which are incorporated herein by reference.

[0045] According to one embodiment, the compound of formula **Ia** is produced as a salt of a sulfonic acid. Exemplary sulfonic acids include methylsulfonic acid, p-toluenesulfonic acid, etc. According to one embodiment, the compound of formula **Ia** is produced as a methylsulfonic acid salt. According to another embodiment, the compound of formula **Ia** is produced as a salt of a dicarboxylic acid. In one embodiment, the dicarboxylic acid is selected from oxalic acid, malonic acid, succinic acid, maleic, or fumaric acid. Or, the dicarboxyclic acid is oxalic acid.

[0046] In certain embodiments, the present invention provides a method for preparing a compound of formula **Ia**:

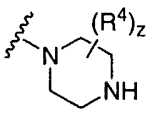


Ia

or a suitable salt thereof;

wherein:

Cy is a ring selected from:



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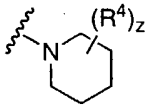

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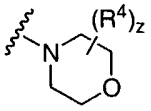

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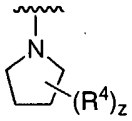

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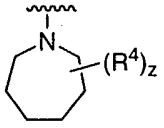

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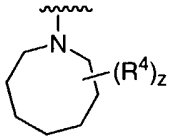

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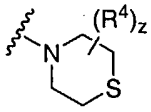
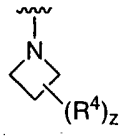


ii



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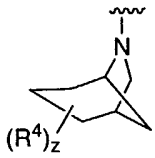

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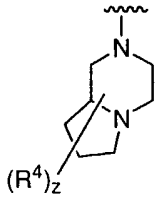

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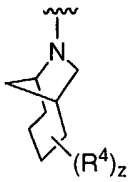

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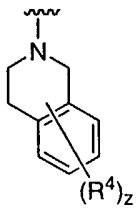


nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', -

SO_2R', $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

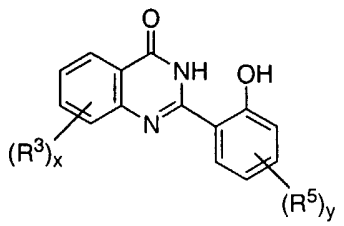
each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

comprising the steps of:

(a) providing a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

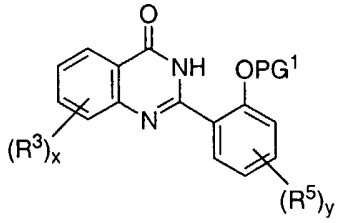
two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

and

(b) converting said compound of formula **II** or a suitable salt thereof to a compound of formula **Ia**.

[0047] In certain embodiments, the method of preparing a compound of formula **Ia** or a suitable salt thereof from a compound of formula **II** or a suitable salt thereof further comprises the steps of:

(a) protecting the hydroxyl group of compound **II** with a suitable hydroxyl protecting group to form a compound of formula **IIa**:



IIa

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

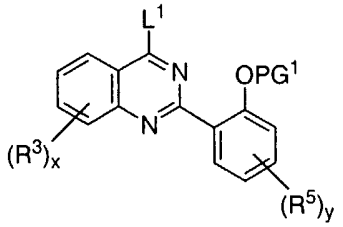
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

(b) converting the the ketone moiety of the compound of formula **IIa** or a suitable salt thereof, to a suitable leaving group to form a compound of formula **IIb**:



IIb

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

L^1 is a suitable leaving group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

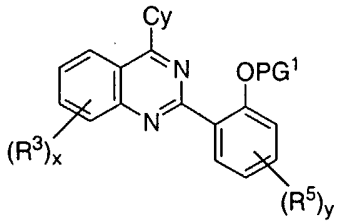
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

(c) displacing said suitable leaving group with a suitable Cy moiety to form a compound of formula **IIc**:



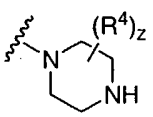
IIc

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is a ring selected from:



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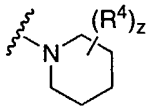

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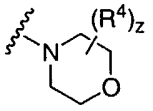

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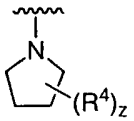

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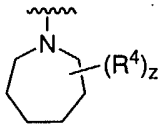

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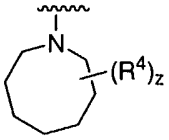

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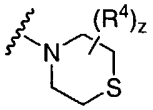
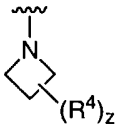


ii



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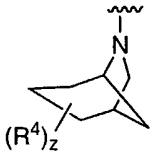

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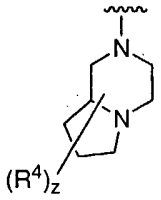

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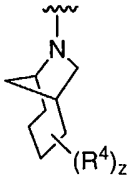

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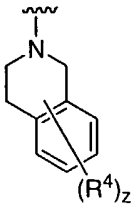


nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', -

SO_2R', $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

and

(d) removing the suitable hydroxyl protecting group to form a compound of formula **Ia** or a suitable salt thereof.

[0048] Suitable hydroxyl protecting groups are well known in the art and include those described in detail in "Protecting Groups in Organic Synthesis", T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Examples of suitable hydroxyl protecting group PG^1 of compounds of formulae **IIa**, **IIb**, and **IIc** further include, but are not limited to, esters, allyl ethers, ethers, silyl ethers,

alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of such esters include formates, acetates, carbonates, and sulfonates. Specific examples include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetyl), crotonate, 4-methoxy-crotonate, benzoate, p-benylbenzoate, 2,4,6-trimethylbenzoate, carbonates such as methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl. Examples of such silyl ethers include trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, and other trialkylsilyl ethers. Alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, allyl, and allyloxycarbonyl ethers or derivatives. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-(trimethylsilyl)ethoxymethyl, and tetrahydropyranyl ethers. Examples of arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, 2- and 4-picolyl. In certain embodiments, the suitable hydroxyl protecting group PG^1 of compounds of formulae **IIa**, **IIb**, and **IIc** is an ester group. In other embodiments, the suitable hydroxyl protecting group PG^1 of compounds of formulae **IIa**, **IIb**, and **IIc** is a pivaloate (trimethylacetyl) group. In certain embodiments, the suitable hydroxyl protecting group PG^1 of compounds of formulae **IIa**, **IIb**, and **IIc** is an ether group. In other embodiments, the suitable hydroxyl protecting group PG^1 of compounds of formulae **IIa**, **IIb**, and **IIc** is a methyl ether group.

[0049] Methods of adding and removing such hydroxyl protecting groups are well-known in the art and available, for example, in P. J. Kocienski, Protecting Groups, Thieme, 1994, (which is hereby incorpoarted in its entirety by reference) and in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, 1999. One of ordinary skill in the art would recognize that the method appropriate to achieve removal of the protecting group of a compound of formula **IIc**, at step (d), depends upon the actual protecting groups used and includes those described by Greene. For example, when said hydroxyl protecting group of a compound of formula **IIc** is an ester group, such removal may be achieved by saponification.

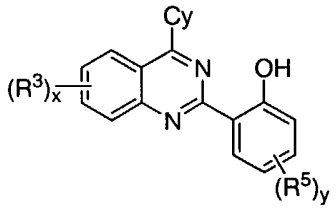
[0050] As used herein, a suitable leaving group is a chemical moiety that is readily displaced by a desired incoming chemical moiety. Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 4th Ed., pp. 351-357, John Wiley and Sons, N.Y. (1992) and "Comprehensive Organic Transformations," Larock,

Richard C., 2nd Ed., John Wiley & Sons, 1999. Examples of suitable leaving group L^1 of formula **IIb** include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyl, optionally substituted alkenylsulfonyl, optionally substituted arylsulfonyl, and diazonium moieties. Examples of suitable leaving group L^1 of formula **IIb** include chloro, iodo, bromo, fluoro, methanesulfonyl (mesyl), tosyl, triflate, nitro-phenylsulfonyl (nosyl), and bromo-phenylsulfonyl (brosyl). In certain embodiments, the suitable leaving group L^1 of formula **IIb** is a halogen group. In other embodiments, the suitable leaving group L^1 of formula **IIb** is a chloro group.

[0051] According to an alternate embodiment, the suitable leaving group may be generated *in situ* within the reaction medium. For example, a leaving group may be generated *in situ* from a precursor of that compound wherein said precursor contains a group readily replaced by said leaving group *in situ*.

[0052] In other embodiments, the preparation of a compound of formula **Ia** from a compound of formula **II** further comprises the step of forming a salt of the compound of formula **Ia**. According to one aspect of the present invention, salt is the oxalic acid salt. According to another aspect of the present invention, the compound of formula **Ia** is treated with oxalic acid to form the oxalic acid salt thereof then that salt is freebased and treated with methanesulfonic acid to form the mesylate salt of a compound of formula **Ia**.

[0053] According to another embodiment, the present invention provides a method for preparing a compound of formula **Ia**:

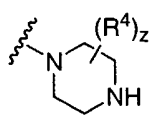


Ia

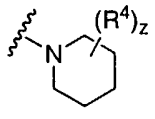
or a suitable salt thereof;

wherein:

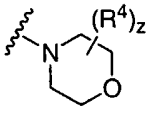
Cy is a ring selected from:



cc



dd



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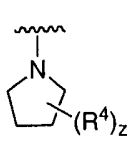

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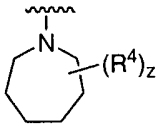

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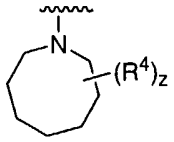

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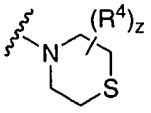
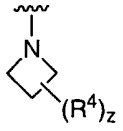
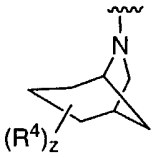


ii



jj



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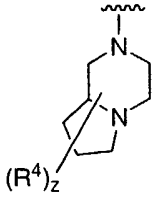

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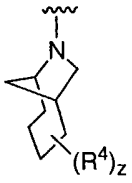

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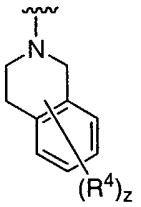


nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $\_NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic,

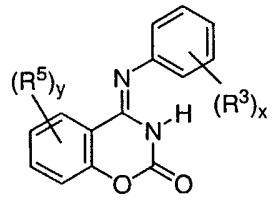
aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

comprising the steps of:

(a) providing a compound of formula **III**:



III

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -$CON(R')_2$, -$OCON(R')_2$, COR', -NHCOOR', -SO_2R', -$SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

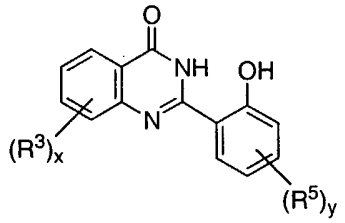
each R^5 is independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR', -CH_2SR', -NRCOR', -$CON(R')_2$, -$S(O)_2N(R')_2$, -OCOR', -COR', -CO_2R', -$OCON(R')_2$, -NR'SO_2R', -$OP(O)(OR')_2$, -$P(O)(OR')_2$, -$OP(O)_2$OR', -$P(O)_2$OR', -$PO(R')_2$, -$OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic,

aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

(b) converting said compound of formula **III** to a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, -OCON(R')$_2$, COR', -NHCOOR', -SO_2R', -SO_2N(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -NRCOR', -CON(R')$_2$, -S(O)$_2$N(R')$_2$, -OCOR', -COR', -CO_2R', -OCON(R')$_2$, -NR'SO_2R', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -OP(O)$_2$OR', -P(O)$_2$OR', -PO(R')$_2$, -OPO(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

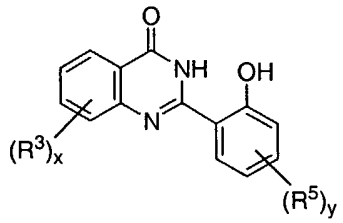
two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

and

(c) converting said compound of formula **II** to a compound of formula **Ia**.

[0054] In certain embodiments, the conversion of a compound of formula **III** to a compound of formula **II**, at step (b), is affected by heating. In other embodiments, step (b) is performed at 150-275 °C. In still other embodiments, step (b) is performed at 200-250 °C in an aprotic solvent. According to another embodiment, step (b) is performed in phenylether.

[0055] According to another embodiment, the present invention provides a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

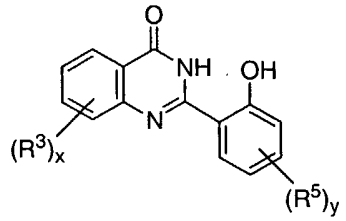
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0056] In certain other embodiments, the present invention provides a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that the following compounds are excluded:

Glycine, N-[2-[2-[6-[bis(carboxymethyl)amino]-2,3-difluorophenoxy]ethoxy]-4-(3,4-dihydro-4-oxo-2-quinazolinyl)-5-hydroxyphenyl]-N-(carboxymethyl)-, tetrapotassium salt;

Glycine, N-[2-[2-[2-[bis(carboxymethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-fluorophenyl]-N-(carboxymethyl)-, tetrapotassium salt;

Glycine, N-[2-[2-[2-[bis(2-methoxy-2-oxoethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-fluorophenyl]-N-(2-methoxy-2-oxoethyl)-, methyl ester;

Glycine, N-[2-[2-[6-[bis(2-methoxy-2-oxoethyl)amino]-2,3-difluorophenoxy]ethoxy]-4-(3,4-dihydro-4-oxo-2-quinazolinyl)-5-hydroxyphenyl]-N-(2-methoxy-2-oxoethyl)-, methyl ester;

Glycine, N-[2-[2-[2-[bis(carboxymethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-methylphenyl]-N-(carboxymethyl)-;

Glycine, N-[2-[2-[2-[bis(carboxymethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-fluorophenyl]-N-(carboxymethyl)-;

4(1H)-Quinazolinone, 6-amino-2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-nitro-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(5-chloro-2-hydroxyphenyl)-:

4(1H)-Quinazolinone, 6-butyl-2-(5-butyl-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-bromo-2-(5-bromo-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-pentylphenyl)-6-pentyl-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxyphenyl)- ;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-methyl-;

4(1H)-Quinazolinone, 6-chloro-2-(5-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-iodo-;

4(1H)-Quinazolinone, 2-(5-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-4-methoxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-nitro-;

4(1H)-Quinazolinone, 6-chloro-2-(5-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(3,5-dichloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-nitrophenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxy-5-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-nitrophenyl)-6-nitro-;

4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxy-5-nitrophenyl)-;

4(1H)-Quinazolinone, 2-(3-fluoro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(3-fluoro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-[5-(1,1-dimethylethyl)-2-hydroxyphenyl]-;

4(1H)-Quinazolinone, 2-(4-hydroxy[1,1'-biphenyl]-3-yl)-;

4(1H)-Quinazolinone, 2-(4-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-3-methylphenyl)-;

4(1H)-Quinazolinone, 2-(3,5-dibromo-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 8-bromo-2-(3,5-dibromo-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6,8-dibromo-2-(3,5-dibromo-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(3,5-dichloro-2-hydroxyphenyl)-;

4(3H)-Quinazolinone, 2-(4-ethoxy-2-hydroxyphenyl)-;

4(3H)-Quinazolinone, 6-chloro-2-(2-hydroxy-m-tolyl)-;

4(3H)-Quinazolinone, 2-(2-hydroxy-m-tolyl)-6-nitro-;

4(3H)-Quinazolinone, 2-(3,5-dichloro-2-hydroxyphenyl)-6-nitro-;

4(3H)-Quinazolinone, 2-(3,5-dichloro-2-hydroxyphenyl)-6-nitro-;

4(1H)-Quinazolinone, 2-(5-chloro-2-hydroxyphenyl)-6-nitro-;

4(3H)-Quinazolinone, 2-(2-hydroxy-5-iodophenyl)-;

4(3H)-Quinazolinone, 6-chloro-2-(2-hydroxy-5-iodophenyl)-;

4(3H)-Quinazolinone, 2-(2-hydroxy-5-iodophenyl)-6-nitro-;

4(3H)-Quinazolinone, 2-(5-bromo-2-hydroxyphenyl)-6-chloro-;

4(3H)-Quinazolinone, 2-(5-bromo-2-hydroxyphenyl)-6-nitro-;

4(3H)-Quinazolinone, 6-chloro-2-(4-ethoxy-2-hydroxyphenyl)-;

4(3H)-Quinazolinone, 2-(4-ethoxy-2-hydroxyphenyl)-6-nitro-;

4(3H)-Quinazolinone, 6-chloro-2-(2,4-dihydroxyphenyl)-;

4(3H)-Quinazolinone, 2-(2,4-dihydroxyphenyl)-6-nitro-;

4(3H)-Quinazolinone, 6-chloro-2-(3,5-dibromo-2-hydroxyphenyl)-;

4(3H)-Quinazolinone, 2-(3,5-dibromo-2-hydroxyphenyl)-6-nitro-;

4(3H)-Quinazolinone, 2-(2-hydroxy-3-biphenylyl)-;

4(3H)-Quinazolinone, 2-(2,5-dihydroxyphenyl)-;

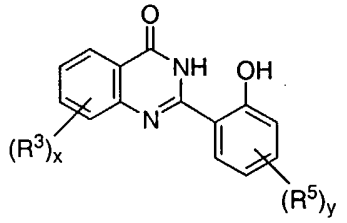
4(3H)-Quinazolinone, 6-chloro-2-(2,5-dihydroxyphenyl)-;

4(3H)-Quinazolinone, 2-(2,5-dihydroxyphenyl)-6-nitro-;

[2-{2-[2-(Carboxymethyl-amino)-5-methyl-phenoxy]-ethoxy}-5-hydroxy-4-(4-hydroxy-quinazolin-2-yl)-phenylamino]-acetic acid; and

[2-{2-[6-(Carboxymethyl-amino)-2,3-difluoro-phenoxy]-ethoxy}-5-hydroxy-4-(4-hydroxy-quinazolin-2-yl)-phenylamino]-acetic acid.

[0057] In certain embodiments, the present invention provides a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

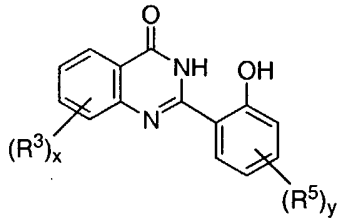
x is 1 or 2;

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy;

y is 0-4; and

each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0058] In other embodiments, the present invention provides a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

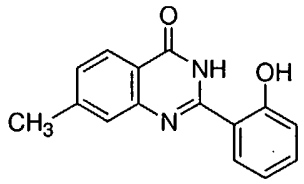
x is 1;

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$;

y is 0 or 1; and

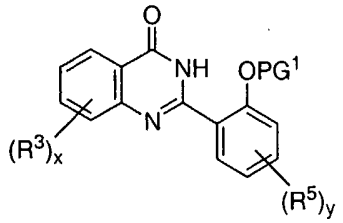
each R^5 is independently Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

[0059] According to another embodiment, the present invention provides compound **II-1** or a suitable salt thereof:



II-1.

[0060] According to another embodiment, the present invention provides a compound of formula **IIa**:



IIa

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

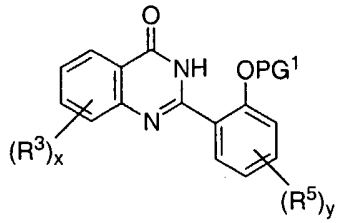
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0061] In certain other embodiments, the present invention provides a compound of formula **IIa**:



IIa

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that the following compounds are excluded:

4(1H)-Quinazolinone, 6-chloro-2-[5-chloro-2-(2,2-dimethoxyethoxy)phenyl]-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2,4-dimethoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2,3-dimethoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2,5-dimethoxyphenyl)-;

Benzoic acid, 4-[(aminoiminomethyl)amino]-, 2-(1,4-dihydro-4-oxo-2-quinazolinyl)phenyl ester, monohydrochloride;

4(1H)-Quinazolinone, 2-[2-(acetyloxy)phenyl]-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-7-(trifluoromethyl)-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-7-methyl-;

4(1H)-Quinazolinone, 2-[2-(acetyloxy)-5-chlorophenyl]-6-chloro-;

6-Quinazolinecarboxylic acid, 2-(2,3-dimethoxyphenyl)-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 2-(5-ethoxy-2-methoxyphenyl)-1,4-dihydro-4-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-[2-methoxy-5-(2-propenyloxy)phenyl]-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-3-methylphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-[2-methoxy-5-(1-methylethoxy)phenyl]-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-5-propoxyphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 2-[5-(2-ethoxyethoxy)-2-methoxyphenyl]-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 2-(3-ethoxy-2-methoxyphenyl)-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxyphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-4-oxo-2-[2-(2-propenyloxy)phenyl]-;

6-Quinazolinecarboxylic acid, 2-[2-(2-ethoxyethoxy)phenyl]-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 2-(2,3-dimethoxyphenyl)-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-3-methylphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-5-methylphenyl)-4-

oxo-;

6-Quinazolinecarboxylic acid, 2-[2-(2-ethoxyethoxy)-3-methoxyphenyl]-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxyphenyl)-4-oxo-, methyl ester;

4(1H)-Quinazolinone, 6,7,8-trimethoxy-2-(2,3,4-trimethoxyphenyl)-;

Carbonic acid, ethyl ester, ester with 2-(o-hydroxyphenyl)-4(3H)-Quinazolinone;

4(3H)-Quinazolinone, 6-butyl-2-(o-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(3,5-dibromo-2-methoxyphenyl)-; and

2-(2'-acetoxyphenyl)-4(3H)-quinazolinone.

[0062] In certain embodiments, the x moiety of formula **IIa** is 1 or 2, and each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

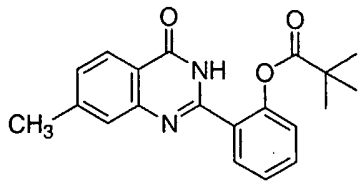
[0063] In other embodiments, the x moiety of formula **IIa** is 1, and R^3 is Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$.

[0064] In still other embodiments, the y moiety of formula **IIa** is 0-4, and each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0065] According to another embodiment, the y moiety of formula **IIa** is 0 or 1, and R^5 is Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

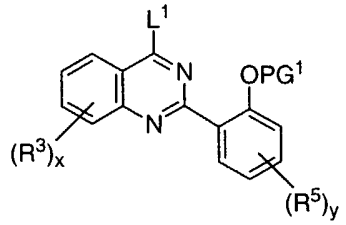
[0066] In other embodiments, the PG^1 group of formula **IIa** is an ester group.

[0067] According to another embodiment, the present invention provides compound **IIa**-1 or a suitable salt thereof:



IIa-1.

[0068] In certain embodiments, the present invention provides a compound of formula **IIb**:



IIb

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

L^1 is a suitable leaving group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully

unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0069] In certain embodiments, the x moiety of formula **IIb** is 1 or 2, and each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

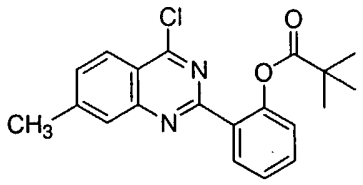
[0070] In other embodiments, the x moiety of formula **IIb** is 1, and R^3 is Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$.

[0071] In still other embodiments, the y moiety of formula **IIb** is 0-4, and each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0072] According to another embodiment, the y moiety of formula **IIb** is 0 or 1, and R^5 is Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

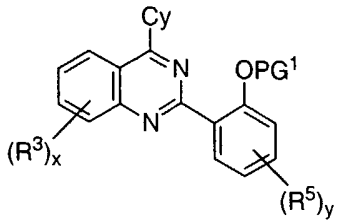
[0073] In other embodiments, the PG^1 group of formula **IIb** is an ester group.

[0074] According to another embodiment, the present invention provides compound **IIb-1** or a suitable salt thereof:



IIb-1.

[0075] According to another aspect, the present invention provides a compound of formula **IIc**:



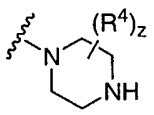
IIc

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is a ring selected from:



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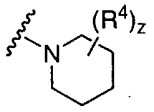
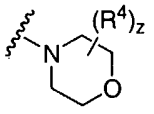
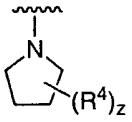


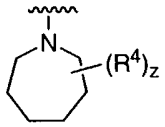
dd



ee



ff



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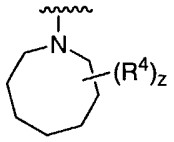

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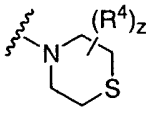
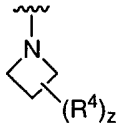


ii



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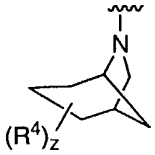

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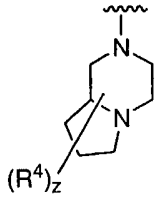

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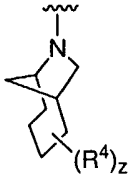

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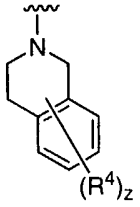

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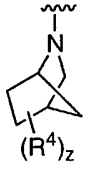


oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl,

heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, -OCON(R')$_2$, COR', -NHCOOR', -SO_2R', -SO_2N(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

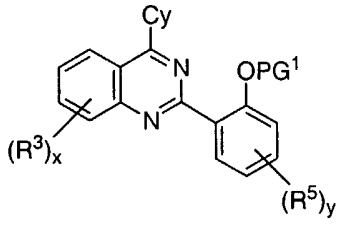
y is 0-5;

each R^5 is independently halogen, CN, NO_2, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -NRCOR', -CON(R')$_2$, -S(O)$_2$N(R')$_2$, -OCOR', -COR', -CO_2R', -OCON(R')$_2$, -NR'SO_2R', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -OP(O)$_2$OR', -P(O)$_2$OR', -PO(R')$_2$, -OPO(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0076] In certain other embodiments, the present invention provides a compound of formula **IIc**:



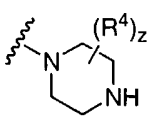
IIc

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is a ring selected from:



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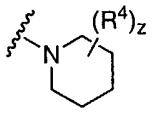

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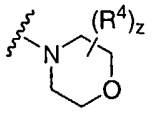
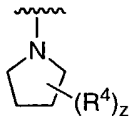


ee



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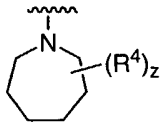

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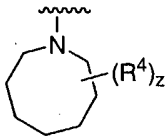

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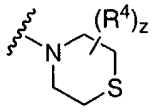
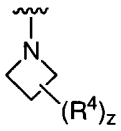
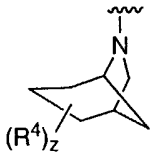


ii



jj



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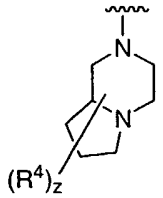

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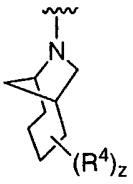

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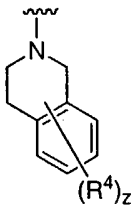


nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl,

heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR', -CH_2SR', -NRCOR', -$CON(R')_2$, -$S(O)_2N(R')_2$, -OCOR', -COR', -CO_2R', -$OCON(R')_2$, -NR'SO_2R', -$OP(O)(OR')_2$, -$P(O)(OR')_2$, -$OP(O)_2$OR', -$P(O)_2$OR', -$PO(R')_2$, -$OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that the following compounds are excluded:

Quinazoline, 2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)-;

Quinazoline, 6-bromo-2-(2-methoxyphenyl)-4-(4-morpholinyl)-;

Quinazoline, 6,8-dichloro-2-(2-methoxyphenyl)-4-(4-morpholinyl)-;

Quinazoline, 6-bromo-2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)-;

Quinazoline, 6,8-dichloro-2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)-;

Quinazoline, 2-(2-fluoro-6-methoxyphenyl)-6-methoxy-4-(4-morpholinyl)-;

Quinazoline, 2-(2-fluoro-6-methoxyphenyl)-4-(4-methyl-1-piperidinyl)-7-(trifluoromethyl)-;

Cyclopropanecarboxylic acid, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Propanoic acid, 2-methyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Butanoic acid, 3-methyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Cyclopentanecarboxylic acid, 3-fluoro-2-[7-methyl-4-(4-methyl-1-

piperidinyl)-2-quinazolinyl]phenyl ester;

Propanoic acid, 2,2-dimethyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Butanoic acid, 3,3-dimethyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Quinazoline, 7-chloro-2-(2-methoxyphenyl)-4-[3-(trifluoromethyl)-1-pyrrolidinyl];

Piperazine, 1-(butylsulfonyl)-4-[2-(2,4-dimethoxyphenyl)-7-methyl-4-quinazolinyl]-;

Phenol, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]-, acetate (ester);

Piperazine, 1-(butylsulfonyl)-4-[2-(2-fluoro-6-methoxyphenyl)-7-(trifluoromethyl)-4-quinazolinyl]-;

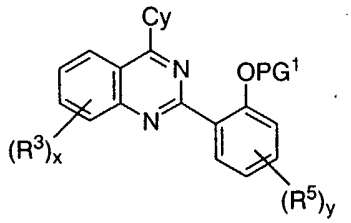
1-Piperazinecarboxylic acid, 4-[6-bromo-2-(2-methoxyphenyl)-4-quinazolinyl]-, 1,1-dimethylethyl ester;

Carbamic acid, (2-methylpropyl)-, 1-[2-(2-methoxyphenyl)-7-methyl-4-quinazolinyl]-4-piperidinyl ester;

6-Quinazolinecarboxylic acid, 4-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-2-(2-methoxyphenyl)-; and

Benzenesulfonamide, 2-methoxy-5-[2-[4-[2-(2-methoxyphenyl)-4-quinazolinyl]-1-piperazinyl]ethyl]-, (2Z)-2-butenedioate (2:3).

[0077] In certain embodiments, the present invention provides a compound of formula **IIc**:



IIc

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is azetidin-1-yl (**jj**), pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), or piperazin-1-yl (**cc**) optionally substituted with 0-4 occurrences of R^4;

each R^4 is independently Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$,

-C(O)NHCH$_2$CH(CH$_3$)$_2$, -C(O)CH(OH)CH$_2$CH(CH$_3$)$_2$, -C(O)CH(OH)CH$_2$C(CH$_3$)$_3$, -NHCOOCH$_3$, -C(O)C(CH$_3$)$_3$, -COO(CH$_2$)$_2$CH$_3$, -C(O)NHCH(CH$_3$)$_2$, -C(O)CH$_2$CH$_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C$_{1-4}$alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, -CH$_2$cyclohexyl, pyridyl, -CH$_2$pyridyl, or -CH$_2$thiazolyl;

x is 1 or 2;

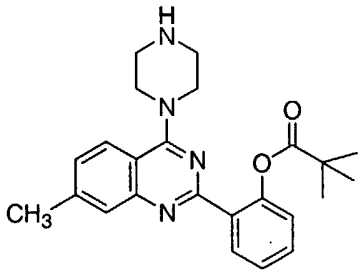
each R^3 is independently Cl, Br, F, CF$_3$, -OCF$_3$, Me, Et, CN, -COOH, -NH$_2$, -N(CH$_3$)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH$_2$)$_2$OCH$_3$, -CONH$_2$, -COOCH$_3$, -OH, -OCH$_3$, -OCH$_2$CH$_3$, -CH$_2$OH, -NHCOCH$_3$, -NHCOCH(CH$_3$)$_2$, -SO$_2$NH$_2$, -CONH(cyclopropyl), -CONHCH$_3$, -CONHCH$_2$CH$_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy;

y is 0-4; and

each R^5 is independently Cl, Br, F, CF$_3$, Me, Et, CN, -COOH, -NH$_2$, –N(CH$_3$)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH$_2$)$_2$OCH$_3$, -CONH$_2$, -COOCH$_3$, -OH, -OCH$_3$, -OCH$_2$CH$_3$, -CH$_2$OH, -NHCOCH$_3$, -SO$_2$NH$_2$, -SO$_2$NHC(CH$_3$)$_2$, -OCOC(CH$_3$)$_3$, -OCOCH$_2$C(CH$_3$)$_3$, -O(CH$_2$)$_2$N(CH$_3$)$_2$, 4-CH$_3$-piperazin-1-yl, OCOCH(CH$_3$)$_2$, OCO(cyclopentyl), -COCH$_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

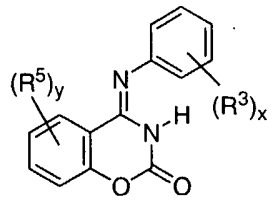
[0078] In other embodiments, the x moiety of formula **IIc** is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, -CH$_3$, -CH$_2$CH$_3$, -F, -CF$_3$, -OCF$_3$, -CONHCH$_3$, -CONHCH$_2$CH$_3$, -CONH(cyclopropyl), -OCH$_3$, -NH$_2$, -OCH$_2$CH$_3$, or -CN. In yet other embodiments, the x moiety of formula **IIc** is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, -CH$_3$, -CH$_2$CH$_3$, -F, -CF$_3$, -OCF$_3$, -OCH$_3$, or -OCH$_2$CH$_3$. In certain other embodiments, the x moiety of formula **IIc** is 1 and R^3 is at the 7-position of the quinazoline ring and is methyl.

[0079] According to another embodiment, the present invention provides compound **IIc**-1 or a suitable salt thereof:



IIc-1.

[0080] According to yet another embodiment, the present invention provides a compound of formula **III**:



III

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

(i) x and y are not simultaneously zero; and

(ii) when y is zero, and x is one, then R^3 is not:

chloro in the para-position; or

methyl in the para-position.

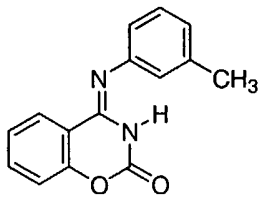
[0081] In certain embodiments, the x moiety of formula **III** is 1 or 2, and each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

[0082] In other embodiments, the x moiety of formula **III** is 1, and R^3 is Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$.

[0083] In still other embodiments, the y moiety of formula **III** is 0-4, and each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

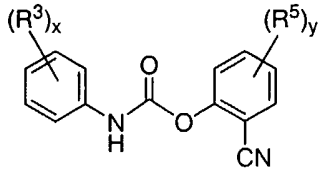
[0084] According to another embodiment, the y moiety of formula **III** is 0 or 1, and R^5 is Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

[0085] According to another embodiment, the present invention provides compound **III**-1 or a suitable salt thereof:



III-1.

[0086] Yet another embodiment of the present invention provides a compound of formula **IV**:



IV

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that when x is one and R^3 is methyl in the 3-position, then when y is one, R^5 is not -S-CN in the 4-position.

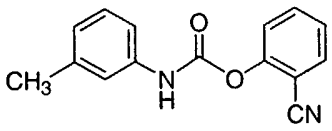
[0087] In certain embodiments, the x moiety of formula **IV** is 1 or 2, and each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

[0088] In other embodiments, the x moiety of formula **IV** is 1, and R^3 is Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$.

[0089] In still other embodiments, the y moiety of formula **IV** is 0-4, and each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0090] According to another embodiment, the y moiety of formula **IV** is 0 or 1, and R^5 is Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

[0091] According to another embodiment, the present invention provides compound **IV**-1 or a suitable salt thereof:



IV-1.

[0092] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

Example 1

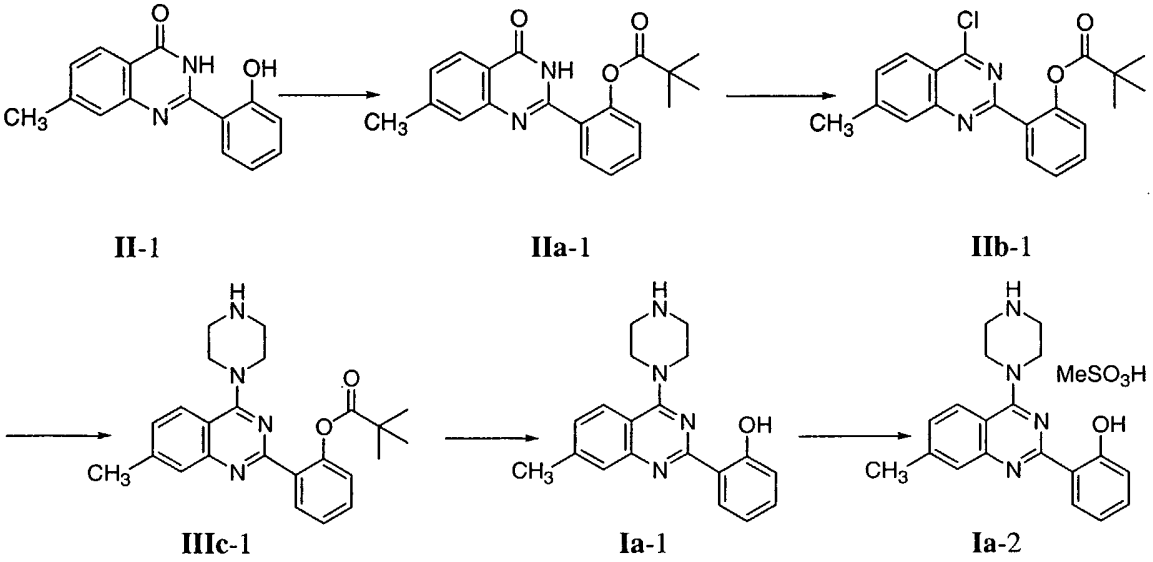
[0093] **4-m-Tolylimino-3,4-dihydro-benzo[e][1,3]oxazin-2-one (III-1)**: 2-Cyanophenol (2.4 g) and m-tolylisocyanate (2.6 g) were combined with toluene (10 mL) and triethylamine (3 drops) and the resulting mixture heated at reflux. After 18 hours, the resulting solid was collected to afford 4.0 g of the title compound.

Example 2

[0094] **2-(2-Hydroxy-phenyl)-7-methyl-3H-quinazolin-4-one (II-1)**: 4-m-Tolylimino-3,4-dihydro-benzo[e][1,3]oxazin-2-one (1.014 g) was combined with diphenyl ether. The resulting mixture was heated at 250°C for 1 hour. The reaction was allowed to cool and the resulting solid was collected to afford 0.91 g of the title compound as a tan solid. ^{1}H-NMR

($CDCl_3$): 8.25 (1H, d), 8.0 (1H, d), 7.55 (1H, s), 7.45 (1H, t), 7.4 (1H, d), 6.85 (1H, d), 6.8 (1H, t).

Example 3



[0095] 2,2-Dimethyl-propionic acid 2-(7-methyl-4-oxo-3,4-dihydro-quinazolin-2-yl)-phenyl ester (IIa-1): 2-(2-Hydroxy-phenyl)-7-methyl-3H-quinazolin-4-one (1.0 g) was suspended in DMF (10 mL). Trimethylacetic anhydride (1.0 mL) and pyridine (0.63 mL) were added and the resulting mixture heated at 50°C for 1 hour. The reaction was poured into water (100 mL) and extracted with methylene chloride (3 x 50 mL). The organic extracts were combined and concentrated *in vacuo* to afford the title compound which was used directly in the next step.

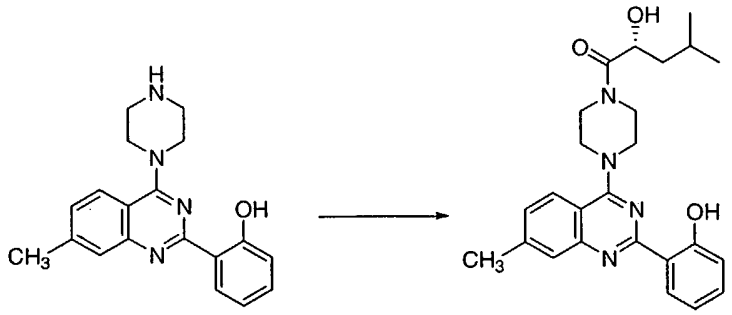
[0096] 2,2-Dimethyl-propionic acid 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenyl ester (IIb-1): The 2,2-dimethyl-propionic acid 2-(7-methyl-4-oxo-3,4-dihydro-quinazolin-2-yl)-phenyl ester prepared above was dissolved in toluene (10 mL) and treated with phosphoryl oxychloride (0.37 mL) and pyridine (0.63 mL). The resulting solution was stirred at 80°C. The reaction was then poured into ice water and extracted with methylene chloride (3 x 50 mL). The combined organic extracts were concentrated *in vacuo* to approximately 20 mL and this concentrate was used directly in the next step.

[0097] 2,2-Dimethyl-propionic acid 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenyl ester (IIIc-1): To the concentrate from above was added piperazine (1.36 g) and triethylamine (3.36 mL). The resulting mixture was allowed to stir. The reaction mixture

was washed with water then concentrated *in vacuo* and the resulting solid used directly in the next step.

[0098] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (Ia-2) and mesylate salt (Ia-3): The solid formed above was dissolved in ethanol (28 mL) and treated with KOH (3.0 g). Upon complete reaction, the mixture was poured into water (100 mL), neutralized with HCl and extracted with methylene chloride (3 x 50 mL). To the resulting solution was added oxalic acid. The resulting solids were collected then freebased and treated with methanesulfonic acid. The resulting solids were recrystallized from ethanol (10 mL) to afford 0.71 g of the mesylate salt as a yellow solid.

Example 4



Ia-2 **7**

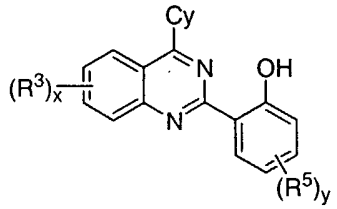
[0099] (R)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (7): A mechanically stirred suspension of 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (**Ia-2**) in DMF (3.6 liters) and N-methylmorpholine (214 ml, 1.2 equivalents) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC, 200g, 1.2 equivalents) and 1-hydroxybenzotriazole hydrate (HOBt, 160g, 1.2 equivalents). A solution of (R)-isocaproic acid (140g, 1.2 equivalents, prepared by methods know in the art from D-leucine) in dimethylformamide (400 ml) was added to the mixture over a period of 6 hours. The mixture was cooled to 0-5°C and water (8 liters) was added slowly to the mixture. The resulting solid was removed from the reaction mixture both manually and via filtration and the solid was then dissolved in THF (2.0 liters), filtered, and treated with methane sulfonic acid (1.2 equivalents). The resulting solid salt was filtered, then dissolved with heating in anhydrous ethanol (3A grade, 4 liters), cooled to 45°C, held at that temperature for 1 hour and then allowed to cool to room temperature. The resulting mesylate was collected by filtration. The salt was then suspended in methylene chloride (2 liters) and treated with potassium carbonate (145.12g, 2 equivalents) previously dissolved in water (2 liters). The organic layer was collected and evaporated to afford a yellow solid,

which after drying under vacuum (125 Torr, room temperature) gave 261.2g of desired product **5** (63% yield) as a yellow solid and as the free base with consistent analytical data.

CLAIMS

We claim:

1. A method for preparing a compound of formula **Ia**:

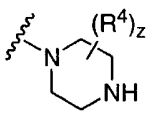


Ia

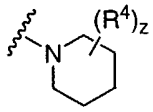
or a suitable salt thereof;

wherein:

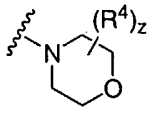
Cy is a ring selected from:



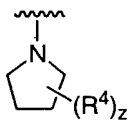
cc



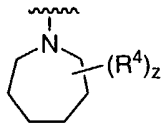
dd



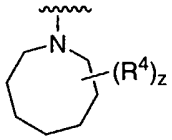
ee



ff



gg



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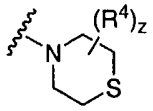
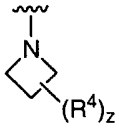
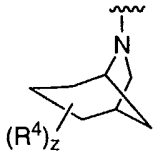


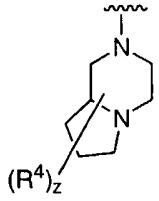
ii



jj



kk



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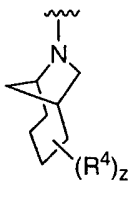
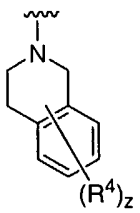


mm



nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

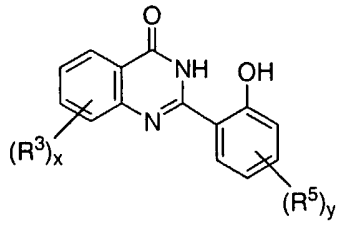
each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

comprising the steps of:

(a) providing a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

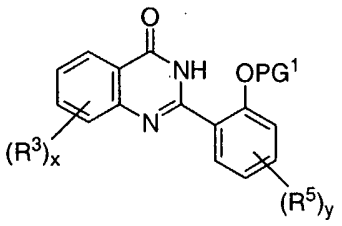
two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

and

(b) converting said compound of formula **II** or a suitable salt thereof, to a compound of formula **Ia** or a suitable salt thereof.

2. The method according to claim 1, further comprising the steps of:

(a) protecting the hydroxyl group of compound **II** with a suitable hydroxyl protecting group to form a compound of formula **IIa**:



IIa

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

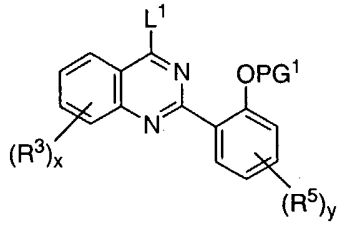
each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially

unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

(b) converting the ketone moiety of the compound of formula **IIa** or a suitable salt thereof, to a suitable leaving group to form a compound of formula **IIb**:



IIb

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

L^1 is a suitable leaving group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

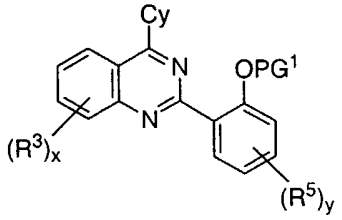
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

(c) displacing said suitable leaving group with a suitable Cy moiety to form a compound of formula **IIc**:



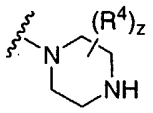
IIc

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is a ring selected from:



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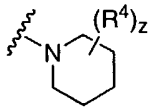

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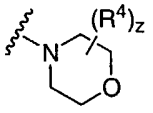

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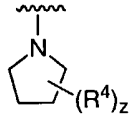

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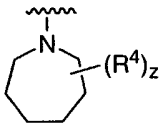

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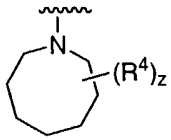
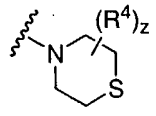
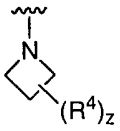


hh



ii



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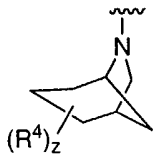

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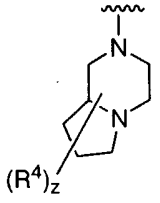
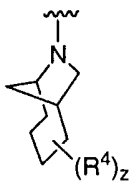


ll



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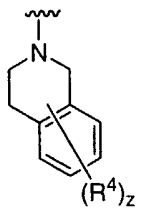


nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

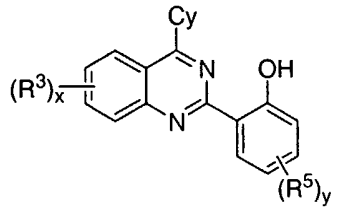
two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

and

(d) removing the suitable hydroxyl protecting group to form a compound of formula Ia.

3. The method according to claim 2, wherein said method further comprises the step of forming a salt of the compound of formula **Ia**.

4. A method for preparing a compound of formula **Ia**:

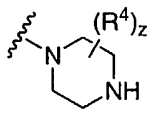


Ia

or a suitable salt thereof;

wherein:

Cy is a ring selected from:



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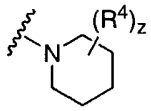

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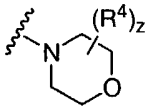
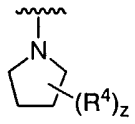


ee



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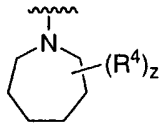

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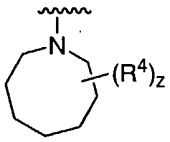

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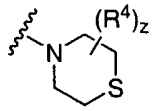
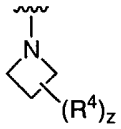


ii



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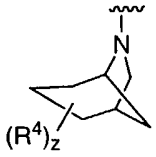

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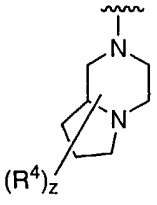

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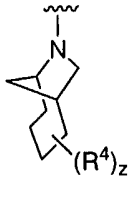

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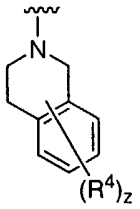


nn

oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

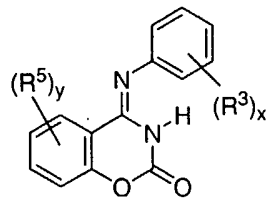
each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, _NR'SO_2R', $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

comprising the steps of:

(a) providing a compound of formula **III**:



III

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

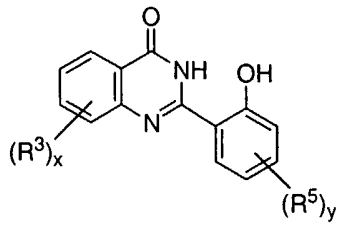
y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

(b) converting said compound of formula **III** or a suitable salt thereof, to a compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

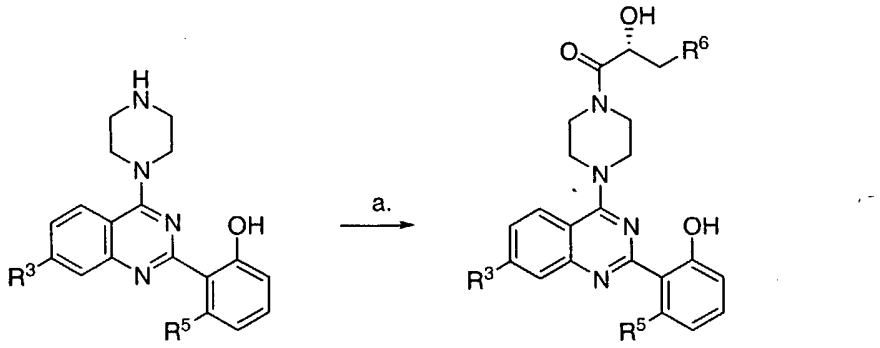
two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

and

(c) converting said compound of formula **II** or a suitable salt thereof, to a compound of formula **Ia** or a suitable salt thereof.

5. The method according to claim 4, wherein the conversion of a compound of formula **III** to a compound of formula **II**, at step (b), is affected by heating.

6. The method according to claim 4 to prepare a compound of formula **V** from a compound of formula **Iaa-1**:



Iaa-1 **V**

comprising the additional step of:

(a) reacting compound of formula **Iaa-1** with (R) isocaproic acid under suitable amide coupling conditions;

wherein R^6 is isopropyl or t-butyl, R^3 is methyl or hydrogen, and R^5 is fluorine or hydrogen.

7. The method according to claim 6, wherein said method further comprises the step of forming a salt of the compound of formula **V**.

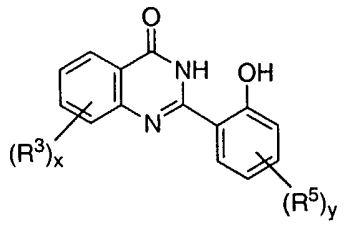
8. The method according to claim 6 or 7, wherein R^6 is isopropyl, R^3 is methyl, and R^5 is hydrogen.

9. The method according to claim 6 or 7, wherein R^6 is t-butyl, R^3 is methyl, and R^5 is hydrogen.

10. The method according to claim 6 or 7, wherein R^6 is isopropyl, R^3 is hydrogen, and R^5 is hydrogen.

11. The method according to claim 6 or 7, wherein R^6 is t-butyl, R^3 is methyl, and R^5 is fluorine.

12. A compound of formula **II**:



II

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that the following compounds are excluded:

Glycine, N-[2-[2-[6-[bis(carboxymethyl)amino]-2,3-difluorophenoxy]ethoxy]-

4-(3,4-dihydro-4-oxo-2-quinazolinyl)-5-hydroxyphenyl]-N-(carboxymethyl)-, tetrapotassium salt;

Glycine, N-[2-[2-[2-[bis(carboxymethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-fluorophenyl]-N-(carboxymethyl)-, tetrapotassium salt;

Glycine, N-[2-[2-[2-[bis(2-methoxy-2-oxoethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-fluorophenyl]-N-(2-methoxy-2-oxoethyl)-, methyl ester;

Glycine, N-[2-[2-[6-[bis(2-methoxy-2-oxoethyl)amino]-2,3-difluorophenoxy]ethoxy]-4-(3,4-dihydro-4-oxo-2-quinazolinyl)-5-hydroxyphenyl]-N-(2-methoxy-2-oxoethyl)-, methyl ester;

Glycine, N-[2-[2-[2-[bis(carboxymethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-methylphenyl]-N-(carboxymethyl)-;

Glycine, N-[2-[2-[2-[bis(carboxymethyl)amino]-5-(1,4-dihydro-4-oxo-2-quinazolinyl)-4-hydroxyphenoxy]ethoxy]-4-fluorophenyl]-N-(carboxymethyl)-;

4(1H)-Quinazolinone, 6-amino-2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-nitro-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(5-chloro-2-hydroxyphenyl)-:

4(1H)-Quinazolinone, 6-butyl-2-(5-butyl-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-bromo-2-(5-bromo-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-pentylphenyl)-6-pentyl-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxyphenyl)- ;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-methyl-;

4(1H)-Quinazolinone, 6-chloro-2-(5-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-iodo-;

4(1H)-Quinazolinone, 2-(5-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-4-methoxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxyphenyl)-6-nitro-;

4(1H)-Quinazolinone, 6-chloro-2-(5-chloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 6-chloro-2-(3,5-dichloro-2-hydroxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-hydroxy-5-nitrophenyl)-;
4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxy-5-methoxyphenyl)-;
4(1H)-Quinazolinone, 2-(2-hydroxy-5-nitrophenyl)-6-nitro-;
4(1H)-Quinazolinone, 6-chloro-2-(2-hydroxy-5-nitrophenyl)-;
4(1H)-Quinazolinone, 2-(3-fluoro-2-hydroxyphenyl)-;
4(1H)-Quinazolinone, 6-chloro-2-(3-fluoro-2-hydroxyphenyl)-;
4(1H)-Quinazolinone, 2-[5-(1,1-dimethylethyl)-2-hydroxyphenyl]-;
4(1H)-Quinazolinone, 2-(4-hydroxy[1,1'-biphenyl]-3-yl)-;
4(1H)-Quinazolinone, 2-(4-chloro-2-hydroxyphenyl)-;
4(1H)-Quinazolinone, 2-(2-hydroxy-3-methylphenyl)-;
4(1H)-Quinazolinone, 2-(3,5-dibromo-2-hydroxyphenyl)-;
4(1H)-Quinazolinone, 8-bromo-2-(3,5-dibromo-2-hydroxyphenyl)-;
4(1H)-Quinazolinone, 6,8-dibromo-2-(3,5-dibromo-2-hydroxyphenyl)-;
4(1H)-Quinazolinone, 2-(3,5-dichloro-2-hydroxyphenyl)-;
4(3H)-Quinazolinone, 2-(4-ethoxy-2-hydroxyphenyl)-;
4(3H)-Quinazolinone, 6-chloro-2-(2-hydroxy-m-tolyl)-;
4(3H)-Quinazolinone, 2-(2-hydroxy-m-tolyl)-6-nitro-;
4(3H)-Quinazolinone, 2-(3,5-dichloro-2-hydroxyphenyl)-6-nitro-;
4(3H)-Quinazolinone, 2-(3,5-dichloro-2-hydroxyphenyl)-6-nitro-;
4(1H)-Quinazolinone, 2-(5-chloro-2-hydroxyphenyl)-6-nitro-;
4(3H)-Quinazolinone, 2-(2-hydroxy-5-iodophenyl)-;
4(3H)-Quinazolinone, 6-chloro-2-(2-hydroxy-5-iodophenyl)-;
4(3H)-Quinazolinone, 2-(2-hydroxy-5-iodophenyl)-6-nitro-;
4(3H)-Quinazolinone, 2-(5-bromo-2-hydroxyphenyl)-6-chloro-;
4(3H)-Quinazolinone, 2-(5-bromo-2-hydroxyphenyl)-6-nitro-;
4(3H)-Quinazolinone, 6-chloro-2-(4-ethoxy-2-hydroxyphenyl)-;
4(3H)-Quinazolinone, 2-(4-ethoxy-2-hydroxyphenyl)-6-nitro-;
4(3H)-Quinazolinone, 6-chloro-2-(2,4-dihydroxyphenyl)-;
4(3H)-Quinazolinone, 2-(2,4-dihydroxyphenyl)-6-nitro-;
4(3H)-Quinazolinone, 6-chloro-2-(3,5-dibromo-2-hydroxyphenyl)-;
4(3H)-Quinazolinone, 2-(3,5-dibromo-2-hydroxyphenyl)-6-nitro-;
4(3H)-Quinazolinone, 2-(2-hydroxy-3-biphenylyl)-;
4(3H)-Quinazolinone, 2-(2,5-dihydroxyphenyl)-;
4(3H)-Quinazolinone, 6-chloro-2-(2,5-dihydroxyphenyl)-;

4(3H)-Quinazolinone, 2-(2,5-dihydroxyphenyl)-6-nitro-;

[2-{2-[2-(Carboxymethyl-amino)-5-methyl-phenoxy]-ethoxy}-5-hydroxy-4-(4-hydroxy-quinazolin-2-yl)-phenylamino]-acetic acid; and

[2-{2-[6-(Carboxymethyl-amino)-2,3-difluoro-phenoxy]-ethoxy}-5-hydroxy-4-(4-hydroxy-quinazolin-2-yl)-phenylamino]-acetic acid.

13. The compound according to claim 12, wherein:

x is 1 or 2;

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy;

y is 0-4; and

each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

14. The compound according to claim 13, wherein:

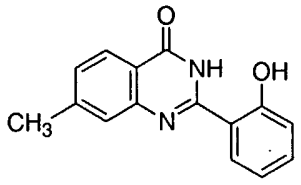
x is 1;

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$;

y is 0 or 1; and

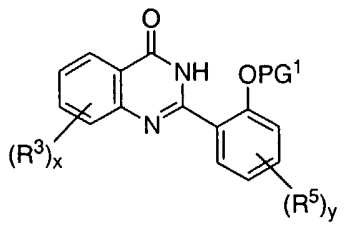
each R^5 is independently Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

15. The compound according to claim 14, wherein said compound is compound **II**-1 or a suitable salt thereof:



II-1.

16. A compound of formula **IIa**:



IIa

or a suitable salt thereof;

wherein:

PG^1 is a suitable hydroxyl protecting group;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that the following compounds are excluded:

4(1H)-Quinazolinone, 6-chloro-2-[5-chloro-2-(2,2-dimethoxyethoxy)phenyl]-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2,4-dimethoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2,3-dimethoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2,5-dimethoxyphenyl)-;

Benzoic acid, 4-[(aminoiminomethyl)amino]-, 2-(1,4-dihydro-4-oxo-2-quinazolinyl)phenyl ester, monohydrochloride;

4(1H)-Quinazolinone, 2-[2-(acetyloxy)phenyl]-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-7-(trifluoromethyl)-;

4(1H)-Quinazolinone, 2-(2-methoxyphenyl)-7-methyl-;

4(1H)-Quinazolinone, 2-[2-(acetyloxy)-5-chlorophenyl]-6-chloro-;

6-Quinazolinecarboxylic acid, 2-(2,3-dimethoxyphenyl)-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 2-(5-ethoxy-2-methoxyphenyl)-1,4-dihydro-4-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-[2-methoxy-5-(2-propenyloxy)phenyl]-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-3-methylphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-[2-methoxy-5-(1-methylethoxy)phenyl]-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-5-propoxyphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 2-[5-(2-ethoxyethoxy)-2-methoxyphenyl]-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 2-(3-ethoxy-2-methoxyphenyl)-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxyphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-4-oxo-2-[2-(2-propenyloxy)phenyl]-;

6-Quinazolinecarboxylic acid, 2-[2-(2-ethoxyethoxy)phenyl]-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 2-(2,3-dimethoxyphenyl)-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-3-methylphenyl)-4-

oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxy-5-methylphenyl)-4-oxo-;

6-Quinazolinecarboxylic acid, 2-[2-(2-ethoxyethoxy)-3-methoxyphenyl]-1,4-dihydro-4-oxo-;

6-Quinazolinecarboxylic acid, 1,4-dihydro-2-(2-methoxyphenyl)-4-oxo-, methyl ester;

4(1H)-Quinazolinone, 6,7,8-trimethoxy-2-(2,3,4-trimethoxyphenyl)-;

Carbonic acid, ethyl ester, ester with 2-(o-hydroxyphenyl)-4(3H)-Quinazolinone;

4(3H)-Quinazolinone, 6-butyl-2-(o-methoxyphenyl)-;

4(1H)-Quinazolinone, 2-(3,5-dibromo-2-methoxyphenyl)-; and

2-(2'-acetoxyphenyl)-4(3H)-quinazolinone.

17. The compound according to claim 16, wherein:

x is 1 or 2; and

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

18. The compound according to claim 17, wherein:

x is 1; and

R^3 is Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$.

19. The compound according to claim 18, wherein:

y is 0-4; and

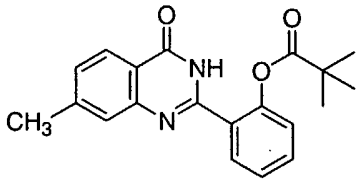
each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

20. The compound according to claim 19, wherein:

y is 0 or 1; and

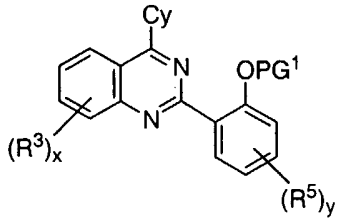
R^5 is Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

21. The compound according to claim 16, wherein said compound is compound **IIa**-1 or a suitable salt thereof:



IIa-1.

22. A compound of formula **IIc**:



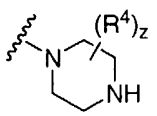
IIc

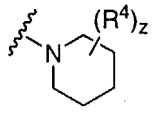
or a suitable salt thereof;

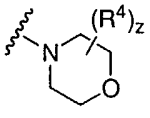
wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is a ring selected from:







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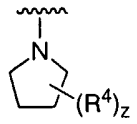
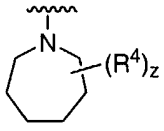
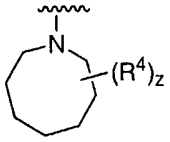
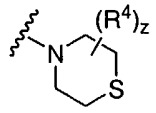
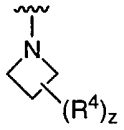
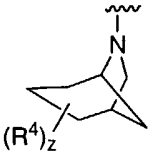
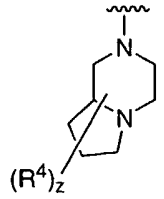
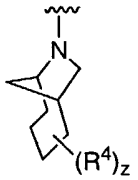
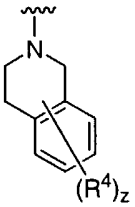




ff gg hh

ii jj kk


ll mm nn oo

and Cy is optionally substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of $-R^4$;

each z is independently 0-5;

each R^4 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$,

or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that the following compounds are excluded:

Quinazoline, 2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)-;

Quinazoline, 6-bromo-2-(2-methoxyphenyl)-4-(4-morpholinyl)-;

Quinazoline, 6,8-dichloro-2-(2-methoxyphenyl)-4-(4-morpholinyl)-;

Quinazoline, 6-bromo-2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)-;

Quinazoline, 6,8-dichloro-2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)-;

Quinazoline, 2-(2-fluoro-6-methoxyphenyl)-6-methoxy-4-(4-morpholinyl)-;

Quinazoline, 2-(2-fluoro-6-methoxyphenyl)-4-(4-methyl-1-piperidinyl)-7-(trifluoromethyl)-;

Cyclopropanecarboxylic acid, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Propanoic acid, 2-methyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Butanoic acid, 3-methyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Cyclopentanecarboxylic acid, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Propanoic acid, 2,2-dimethyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Butanoic acid, 3,3-dimethyl-, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]phenyl ester;

Quinazoline, 7-chloro-2-(2-methoxyphenyl)-4-[3-(trifluoromethyl)-1-

pyrrolidinyl];

Piperazine, 1-(butylsulfonyl)-4-[2-(2,4-dimethoxyphenyl)-7-methyl-4-quinazolinyl]-;

Phenol, 3-fluoro-2-[7-methyl-4-(4-methyl-1-piperidinyl)-2-quinazolinyl]-, acetate (ester);

Piperazine, 1-(butylsulfonyl)-4-[2-(2-fluoro-6-methoxyphenyl)-7-(trifluoromethyl)-4-quinazolinyl]-;

1-Piperazinecarboxylic acid, 4-[6-bromo-2-(2-methoxyphenyl)-4-quinazolinyl]-, 1,1-dimethylethyl ester;

Carbamic acid, (2-methylpropyl)-, 1-[2-(2-methoxyphenyl)-7-methyl-4-quinazolinyl]-4-piperidinyl ester;

6-Quinazolinecarboxylic acid, 4-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-2-(2-methoxyphenyl)-; and

Benzenesulfonamide, 2-methoxy-5-[2-[4-[2-(2-methoxyphenyl)-4-quinazolinyl]-1-piperazinyl]ethyl]-, (2Z)-2-butenedioate (2:3).

23. The compound according to claim 22, wherein:

PG^1 is a suitable hydroxyl protecting group;

Cy is azetidin-1-yl (**jj**), pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), or piperazin-1-yl (**cc**) optionally substituted with 0-4 occurrences of R^4;

each R^4 is independently Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-C(O)CH(OH)CH_2CH(CH_3)_2$, $-C(O)CH(OH)CH_2C(CH_3)_3$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, $-CH_2$cyclohexyl, pyridyl, $-CH_2$pyridyl, or $-CH_2$thiazolyl;

x is 1 or 2;

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy;

y is 0-4; and

each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

24. The compound of claim 16, wherein:

x is 1; and

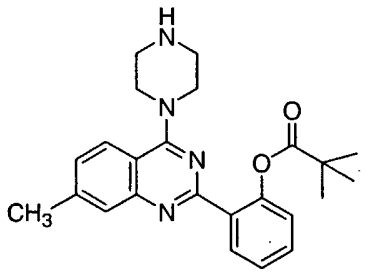
R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or –CN.

25. The compound according to claim 24, wherein:

x is 1; and

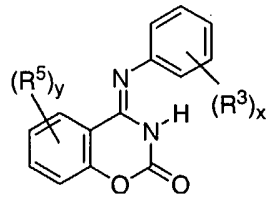
R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$

26. The compound according to claim 25, wherein said compound is compound **IIc**-1 or a suitable salt thereof:



IIc-1.

27. A compound of formula **III**:



III

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

(i) x and y are not simultaneously zero; and

(ii) when y is zero, and x is one, then R^3 is not:

chloro in the para-position; or

methyl in the para-position.

28. The compound according to claim 27, wherein:

x is 1 or 2; and

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$,

-$CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

29. The compound according to claim 28, wherein:

x is 1; and

R^3 is Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, -OH, or $-OCH_3$.

30. The compound according to claim 29, wherein:

y is 0-4; and

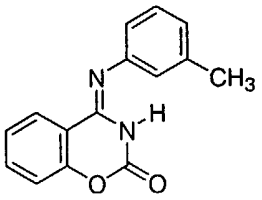
each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

31. The compound according to claim 30, wherein:

y is 0 or 1; and

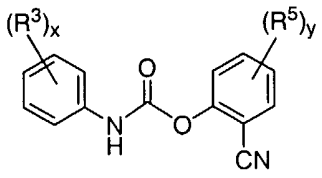
R^5 is Cl, Br, F, CF_3, Me, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$.

32. The compound according to claim 31, wherein said compound is compound **III**-1 or a suitable salt thereof:



III-1.

33. A compound of formula **IV**:



IV

or a suitable salt thereof;

wherein:

x is 0-4;

each R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl;

y is 0-5;

each R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl; and

each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that when x is one and R^3 is methyl in the 3-position, then when y is one, R^5 is not -S-CN in the 4-position.

34. The compound according to claim 33, wherein:

x is 1 or 2; and

each R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$,

-$CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

35. The compound according to claim 34, wherein:

x is 1; and

R^3 is Cl, Br, F, CF_3, -OCF_3, Me, Et, CN, -COOH, -OH, or -OCH_3.

36. The compound according to claim 35, wherein:

y is 0-4; and

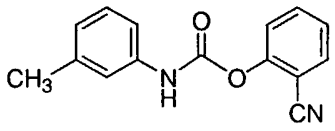
each R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, -NH_2, –$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -CH_2OH, -$NHCOCH_3$, -SO_2NH_2, -$SO_2NHC(CH_3)_2$, -$OCOC(CH_3)_3$, -$OCOCH_2C(CH_3)_3$, -$O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), -$COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

37. The compound according to claim 36, wherein:

y is 0 or 1; and

R^5 is Cl, Br, F, CF_3, Me, -OH, -OCH_3, -OCH_2CH_3, -CH_2OH, -$NHCOCH_3$, -SO_2NH_2, -$SO_2NHC(CH_3)_2$.

38. The compound according to claim 37, wherein said compound is compound **IV**-1 or a suitable salt thereof:



IV-1.