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(54) Title: HETEROCYCLIC AND BICYCLIC COMPOUNDS, COMPOSITIONS AND METHODS

(57) Abstract: The present invention provides, among other things, new bicyclo heterocyclic compounds, compositions comprising these heterocyclic compounds, methods of making the heterocyclic compounds, and methods of using these heterocyclic compounds for treating a variety of conditions and disease states associated with, for example, cellular proliferation, inflammation, glycosidase expression, or the low expression of Perlecan.

HETEROCYCLIC AND BICYCLIC COMPOUNDS, COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

The present invention relates to bicyclo heterocyclic compounds, methods and compositions for making and using the heterocyclic compounds, and methods for treating conditions or diseases associated with cellular proliferation, inflammation, or glycosidase expression.

BACKGROUND OF THE INVENTION

Novel compounds for new therapeutic interventions are needed for many areas of medicine and disease treatment. For example, chronic and acute inflammatory conditions form the basis for diseases affecting all organ systems including, but not limited to, asthma, acute inflammatory diseases, vascular inflammatory disease, chronic inflammation, atherosclerosis, angiopathy, myocarditis, nephritis, Crohn's disease, arthritis, type I and II diabetes and associated vascular pathologies. The incidence of these inflammatory conditions is on the rise in the population as a whole, with diabetes alone affecting 16 million people. Therefore, synthesis of novel compounds leads to new possibilities for discovery of novel therapeutic interventions.

While inflammation in and of itself is a normal immune response, chronic inflammation leads to complications and ongoing system damage due to the interactions of unknown cellular factors. In particular, chronic inflammation can cause endothelial damage resulting in vascular complications. Coronary artery, cerbrovascular and peripheral vascular disease resulting from atherosclerotic and thromboembolic macroangiopathy are the primary causes of mortality in chronic inflammatory diseases.

Many humans and animals have limited lifespans and lifestyles because of conditions relating to lifestyle choices, such as diet and exercise, or because of genetic predispositions to develop a disease. For example, vascular smooth muscle cell (SMC) proliferation is a common consequence of endothelial injury and is believed to be an early pathogenetic event in the formation of atherosclerotic plaques or complications related to vascular injury or as a result surgical interventions. Abnormal vascular SMC proliferation is thought to contribute to the pathogenesis of vascular occlusive lesions, including arteriosclerosis, atherosclerosis, restenosis, and graft atherosclerosis after organ transplantation.

One disease that rapidly growing in the industrialized countries is the occurrence of diabetes and all of its attendant sequellae. One of the factors important in the damage associated with diabetes is the presence of glycated proteins. Glycated proteins and advanced glycation end products (AGE) contribute to cellular damage, particularly, diabetic tissue injury. One potential mechanism by which hyperglycemia can be linked to microangiopathies is through the process of non-enzymatic glycation of critical proteins. These are a highly reactive group of molecules whose interaction with specific receptors on the cell-surface which are thought to lead to pathogenic outcomes.

Another major area of unwanted cellular growth, that is unchecked by the body's regulatory systems, is cancer or oncological conditions. Many therapies have been used and are being used in an effort to restore health or at least stop the unwanted cell growth. Many times, therapeutic agents can have an effect individually, but often, therapeutic regimes require combinations of different pharmacological agents with treatments such as surgery or radiation.

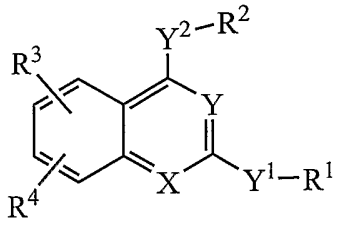
There is a present need for treatments of chronic or acute diseases, such as atherosclerosis, unwanted cellular growth or cellular proliferation, diabetes, inflammatory conditions and vascular occlusive pathologic conditions. Because of occurrence is frequent, the currently available treatments are costly and the conditions are refractory to many pharmacological therapies. The mechanisms involved in the control or prevention of such diseases are not clear and there exists a need for preventive and therapeutic treatments of these and other diseases. Thus, what is

presently needed are novel compounds that find utility in methods and compositions for treatment and prevention of chronic and acute diseases.

SUMMARY OF THE INVENTION

The present invention is directed to novel bicycle (or bicyclic) heterocyclic compounds, novel compositions comprising these heterocyclic compounds, and novel methods employing such bicyclo heterocycles and their compositions. Disclosed herein are methods for making bicyclo heterocyclic compounds, compositions comprising these heterocycles, and methods and compositions for using these bicyclic heterocycles. The heterocyclic compounds and compositions comprising these compounds have utility in treatment of a variety of diseases.

In one aspect, the present invention provides for compounds and compositions comprising these compounds, in which the compounds have the following formula:



(I);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

X and Y are selected independently from CH or N, with a proviso that at least one of X or Y represents N;

Y^1 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl, alkoxy, or haloalkyl, any of which having up to 12 carbon atoms, halogen, or hydrogen;

R^5 is a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

any of R^1, R^2, and R^5 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, $-CO_2R^6$, $-COR^8$, $-CONR^6R^7$, $-SO_2R^8$ and $-SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

when R^3 and R^4 are selected independently from an alkyl, an alkoxy, or a haloalkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from an alkyl having up to 12 carbon atoms, hydroxyl, or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

In the compound of formula **I**, any optional substituents on any group R^1, R^2, R^3, R^4, and R^5 are selected independently of any other substituents, therefore, substituents can occur none, one, two, three, or more times, as each group R^1, R^2, R^3, R^4, and R^5 allows, and the substituents selected can be the same or can be different.

The present invention also is directed to a method for treating a condition or disease in a mammalian subject, including a human. In some aspects, the method comprises administering to the subject a composition comprising a therapeutically-effective amount of at least one compound disclosed herein, or their pharmaceutically-acceptable salts thereof. In some aspects, the at least one compound is, for example, formula I, II, IIa, IIb, IIc, IId, IIe, II-1, III, IIIa, III-1, IV, IVa, IV-1, Va, Vb,Vc, Vd, Ve,

Vf, VIa, VIb, VIc, VId, VIe, VIf, VIIa, VIIb, VIIc, VIId, VIIe, VIIf, VIIIa, IXa, Xa, XI, XII, XIII, or any combination thereof.

Besides being useful for treating a human subject, the methods and compositions of the present invention are useful for treating a variety of mammals such as, for example, companion animals (*e.g.*, cat, dog), primates, ruminant animals, and rodents.

The present invention also is directed to a method for treating a condition or disease associated with a cellular proliferation in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound disclosed herein, or their pharmaceutically-acceptable salts thereof. In some aspects, the at least one compound is, for example, formula I, II, IIa, IIb, IIc, IId, IIe, II-1, III, IIIa, III-1, IV, IVa, IV-1, Va, Vb,Vc, Vd, Ve, Vf, VIa, VIb, VIc, VId, VIe, VIf, VIIa, VIIb, VIIc, VIId, VIIe, VIIf, VIIIa, IXa, Xa, XI, XII, XIII, or any combination thereof. Also in some aspects, the condition or disease is a neoplasia. In another aspect, the condition or disease is SMC hyperplasia.

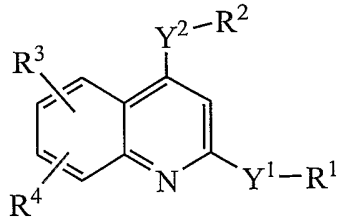
The present invention also is directed to a method for treating a condition or disease related to glycosidase expression. In one aspect, the present invention provides a method for treating a condition or disease associated with glycosidase expression in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound disclosed herein, or their pharmaceutically-acceptable salts thereof. In some aspects, the at least one compound is, for example, formula I, II, IIa, IIb, IIc, IId, IIe, II-1, III, IIIa, III-1, IV, IVa, IV-1, Va, Vb,Vc, Vd, Ve, Vf, VIa, VIb, VIc, VId, VIe, VIf, VIIa, VIIb, VIIc, VIId, VIIe, VIIf, VIIIa, IXa, Xa, XI, XII, XIII, or any combination thereof.

The present invention also is directed to a method for treating a condition or disease associated with an inflammation in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound disclosed herein, or their pharmaceutically-acceptable salts thereof. In some aspects, the at least one compound is, for example, formula I, II, IIa, IIb, IIc, IId, IIe, II-1, III, IIIa, III-1, IV, IVa, IV-1, Va, Vb,Vc, Vd, Ve,

Vf, VIa, VIb, VIc, VId, VIe, VIf, VIIa, VIIb, VIIc, VIId, VIIe, VIIf, VIIIa, IXa, Xa, XI, XII, XIII, or any combination thereof. In one aspect, the therapeutically effective amount is sufficient to attenuate or inhibit inflammation. In some aspects, the inflammation is associated with accumulation or presence of glycated proteins or AGE.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, novel bicyclic heterocyclic compounds and novel compositions comprising these heterocyclic compounds are described. In one aspect, compounds in accordance with the present invention can comprise bicyclo heterocyclic compounds, having the following formula:



(II);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is $>NR^5$ or a direct a bond between the 6-membered ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the 6-membered ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl, alkoxy, or haloalkyl, any of which having up to 12 carbon atoms, halogen, or hydrogen;

R^5 is a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

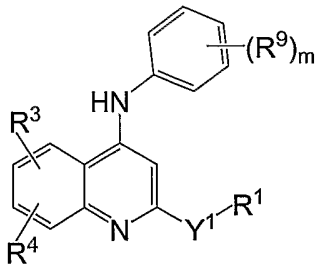
any of R^1, R^2, and R^5 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, $-CO_2R^6$, $-COR^8$, $-CONR^6R^7$, $-SO_2R^8$ and $-SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

any of R^3 and R^4 is optionally substituted with at least one group selected independently from an alkyl having up to 12 carbon atoms, hydroxyl, or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

In yet another aspect, the present invention provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:



(IIa);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

R^1 is a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^9, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a cycloalkyl, a haloalkoxy, any of which having up to 12 carbon atoms; or 2) halogen or hydroxyl;

m is an integer from 0 to 3, inclusive;

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, $CONR^6R^7$, $-SO_2R^8$, or $-SO_2NR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

Further to this aspect and the formula (**IIa**) presented immediately above, the following substituents of the formula can be selected as follows, while unspecified substitutents are selected as above:

Y^1 is a direct a bond between the heterocyclic ring and R^1;

m is an integer from 0 to 2, inclusive;

R^1 is a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

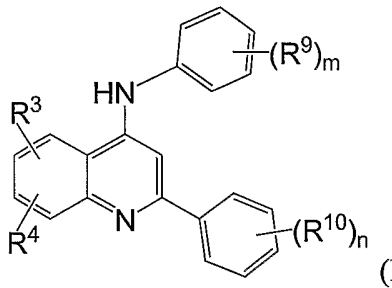
R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, $CONR^6R^7$, $-SO_2R^8$, or $-SO_2NR^6R^7$, any of which having up to 12 carbon atoms; or 2) halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

Further to this aspect and the formula (**IIa**) presented above, the following substituents of the formula can be selected as follows, while unspecified substitutents are selected as above: R^1 can be a substituted or an unsubstituted heterocyclyl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms; comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$.

In still a further aspect, the present disclosure provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:



(**IIb**);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^9, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a cycloalkyl, a haloalkoxy, any of which having up to 12 carbon atoms; or 2) halogen or hydroxyl;

R^{10}, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an an alkylthio, a haloalkyl, a cycloalkyl, a haloalkoxy, SO_2R^8, $SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; or 2) halogen;

m and n are independently an integer from 0 to 3, inclusive;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

In a further aspect of the invention, this disclosure provides heterocyclic compounds, wherein the compound is selected from any of the following compounds:

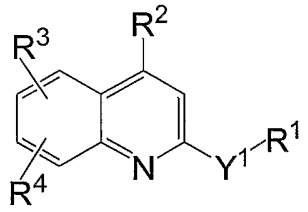
(3-chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine;

(3-chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine;

(4-chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine; or

any combination thereof.

One more aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:



(IIc);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, SO_2R^8, $-SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least

one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^2 is optionally substituted with at least one group selected independently from:

1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, -$SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

In yet another aspect regarding formula (**IIc**) presented above, the following substituents of the formula can be selected as provided here, while unspecified substitutents are selected as indicated above for formula (**IIc**):

Y^1 is >NH; and

R^1 is selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$.

In a further aspect regarding formula (**IIc**) presented immediately above, the following substituents of the formula can be selected as provided here, while unspecified substitutents are selected as indicated above for formula (**IIc**): R^1 is a substituted or an unsubstituted heterocyclyl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$.

In a further aspect regarding formula (**IIc**) presented immediately above, the following substituents of the formula can be selected as provided here, while

unspecified substitutents are selected as indicated above for formula (**IIc**): R^1 is a substituted or an unsubstituted heteroaryl having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6.

In still a further aspect, the present disclosure provides compounds and compositions comprising these compounds, wherein the compound is 2-benzo[1,3]-dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline.

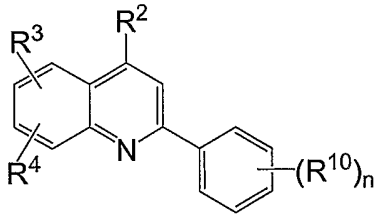
Still another aspect of this invention regarding formula (**IIc**) presented above, the following substituents of the formula can be selected as provided here, while unspecified substitutents are selected as indicated above for formula (**IIc**):

Y^1 is a direct a bond between the heterocyclic ring and R^1;

R^1 is a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6; and

R^2 is a substituted or an unsubstituted heteroaryl having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6.

An additional aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:



(IId);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^2 is selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, >NR^6, >SO_2, or >CO;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^2 is optionally substituted with at least one group selected independently from:

1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, -$SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^{10}, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, -$SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

n is an integer from 0 to 2, inclusive;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

In still a further aspect regarding formula (**IId**) presented above, the following substituents of the formula can be selected as provided here, while unspecified substitutents are selected as indicated above for formula (**IId**): R^2 can be a substituted or an unsubstituted pyrazole, imidazole or indole. In this aspect, R^2 is optionally substituted with at least one group selected as indicated for formula (**IId**).

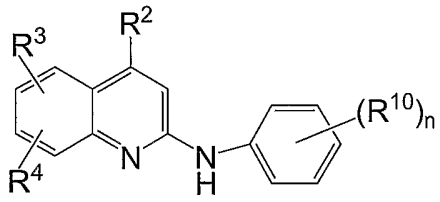
In still a further aspect, this invention provides compounds, and compositions comprising the compounds, wherein the compound is selected from:

2-(4-fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline; or any combination thereof.

One more aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:



(**IIe**);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^2 is a substituted or an unsubstituted heteroaryl having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^{10}, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, SO_2R^8, $-SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

n is an integer from 0 to 2, inclusive;

R^2 is optionally substituted with at least one group selected independently from:

1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, -$SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

In a further aspect of the invention, this disclosure provides heterocyclic compounds, wherein the compound is selected from any of the following:

(4-methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine;

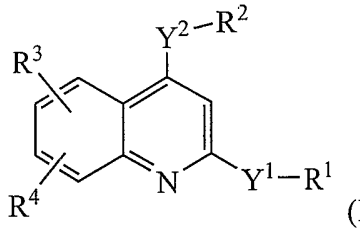
(4-trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine;

N-methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide;

N-methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide; or

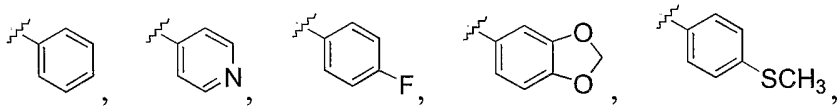
any combination thereof.

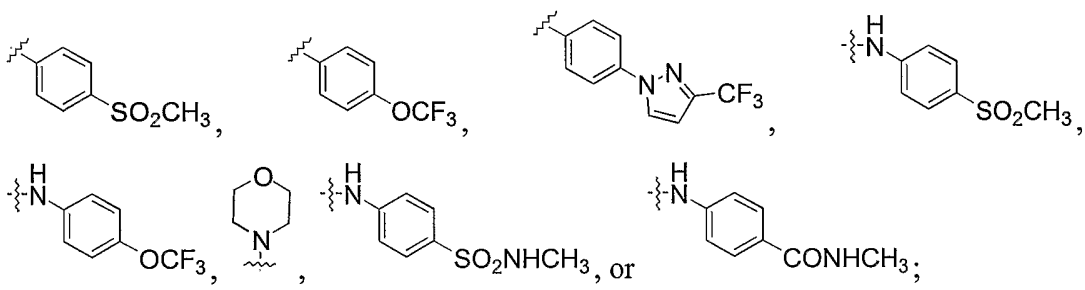
In yet an additional or a further aspect, the present invention provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:

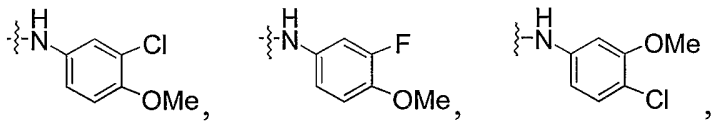


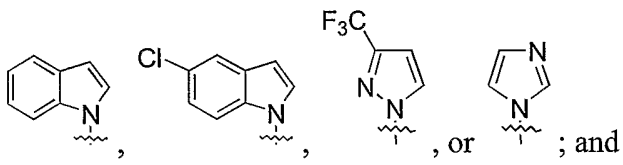
(II-1);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is 



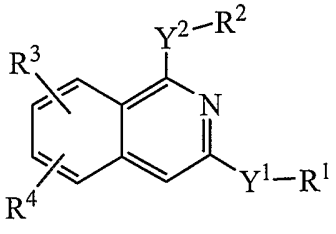
Y^2R^2 represents 



; and

R^3 and R^4 are hydrogen.

In yet another aspect, the present invention provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:



(III);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

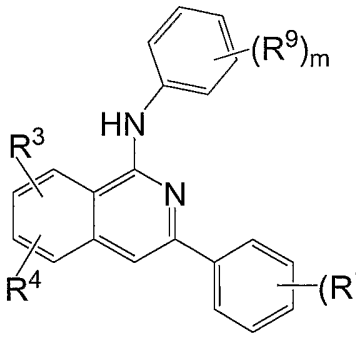
R^1 and R^2 are optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen;

R^8 is an alkyl or aryl having up to 12 carbon atoms; and

when R^3 or R^4 are independently an alkyl, R^3 or R^4 are optionally substituted with at least one group selected independently from hydroxyl or halogen.

An additional aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:



(IIIa);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

R^9 and R^{10}, in each occurrence, are selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

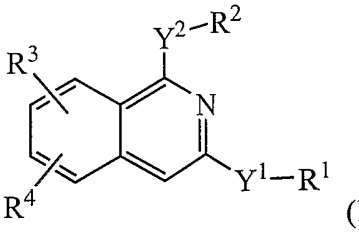
m and n are independently an integer from 0 to 3, inclusive;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

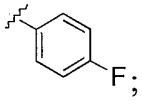
R^8 is an alkyl or aryl having up to 12 carbon atoms.

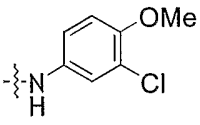
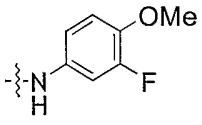
In still a further aspect, this invention provides compounds, and compositions comprising the compounds, wherein the compound is (3-fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine.

Another aspect of the present invention provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:


(III-1);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

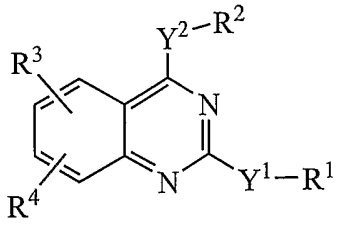
Y^1R^1 is  ;

Y^2R^2 is  or  ;

R^3 is CH_3; and

R^4 is hydrogen.

In still another aspect, the present invention provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:


(IV);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

Y^2 is >NH or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

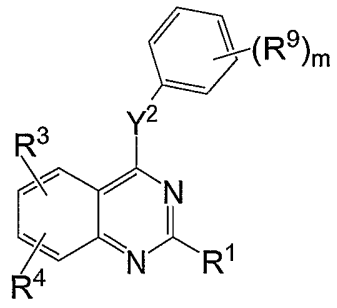
R^1 and R^2 are optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

when R^3 and R^4 are selected independently from an alkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from hydroxyl or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

One more aspect of this invention provides for heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:



(IVa);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^2 is >NH or a direct a bond between the heterocyclic ring and R^2;

R^1 is a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^9, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, or a haloalkoxy, any of which having up to 12 carbon atoms; or 2) halogen or hydroxyl;

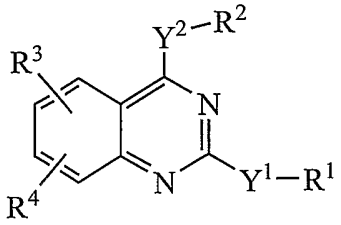
m is an integer from 0 to 2, inclusive;

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen; and

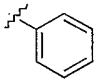
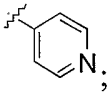
when R^3 and R^4 are selected independently from an alkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from hydroxyl, or halogen.

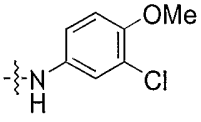
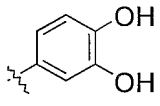
Still another aspect of the present invention provides compounds and compositions comprising these compounds, wherein the compounds have the following formula:



(IV-1);

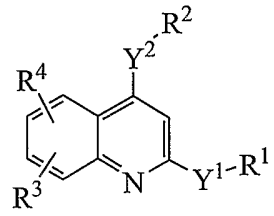
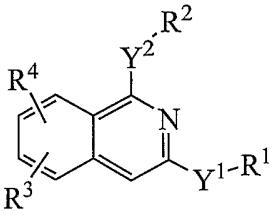
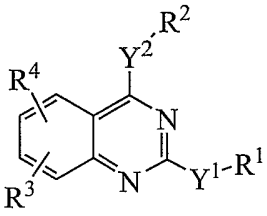
or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is  or  ;

Y^2R^2 is  or  ; and

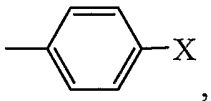
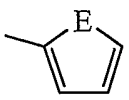
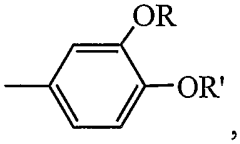
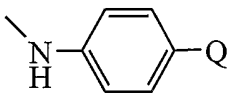
R^3 and R^4 are hydrogen.

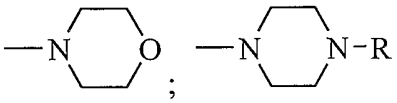
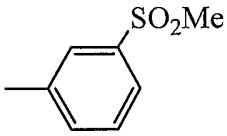
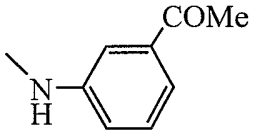
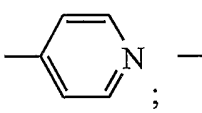
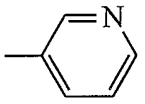
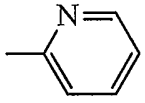
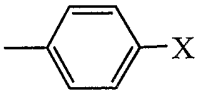
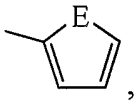
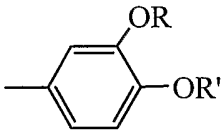
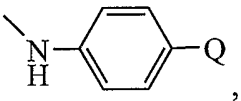
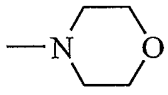
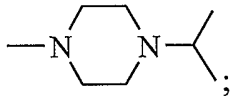
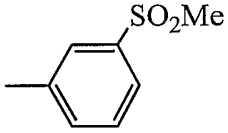
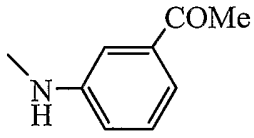
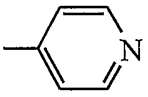
An additional aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

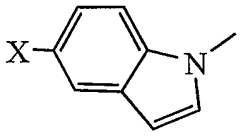
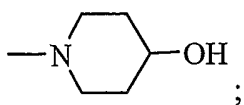
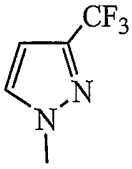
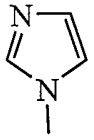
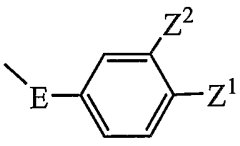
 **(Va)**,  **(VIa)**, or 

(VIIa);

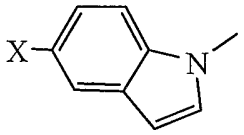
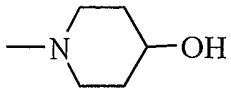
or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

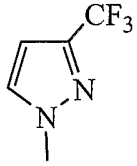
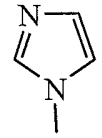
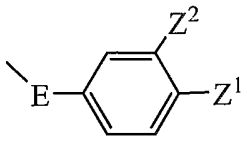
In this aspect, Y^1R^1 can be selected from:  , wherein X is selected from H, F, Cl, Br, I, OMe, OEt, OPh, or CONHMe;  , wherein E is selected from O, S, NH, or NMe;  , wherein R and R' are selected independently from Me, Et, Pr, Bu, or Ph;  , wherein Q is selected

from SO_2Me or $NHSO_2Me$;  ; , wherein R is selected independently from Me, Et, Pr, Bu, or Ph;  ;  ;  ;  ; or  . Further, Y^1R^1 also can be selected from:  , wherein X is selected from H, F, Cl, Br, I, OMe, OEt, or CONHMe;  , wherein E is selected from O of NH;  , wherein R and R' are selected independently from Me or Et;  , wherein Q is selected from SO_2Me or $NHSO_2Me$;  ;  ;  ;  or  .

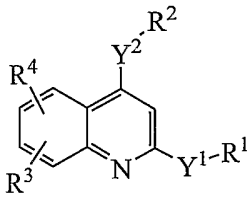
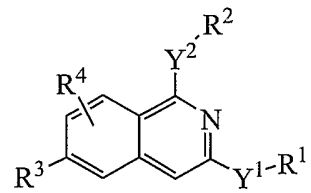
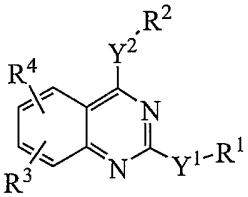
Also in this aspect, Y^2R^2 can be selected from: NR_2, wherein R is selected from Me or Et;  , wherein X is selected from H or Cl;  ;  ,  ; or  , wherein E is selected from >O or >NH; Z^1 and Z^2 are selected independently from H, F, Cl, Br, I, Me, Et, Pr, Bu, Ph, OH, OMe, OEt, OPr, OBu, OPh, SMe, SEt, SPr, SBu, SPh, SO_2Me, SO_2Et, SO_2Pr, SO_2Bu, or SO_2Ph; or Z^1 and Z^2 together are a fused 1,3-dioxolane ring.

Further, Y^2R^2 also can be selected from: NR_2, wherein R is selected from Me or Et;


, wherein X is selected from H or Cl;

;

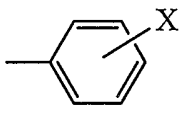
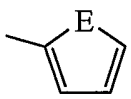
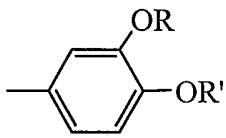

, 
; or 
, wherein E is selected from >O or >NH; Z^1 is selected from H, OH, OMe, SMe, or SO_2Me; Z^2 is selected from H, F, Cl, Me, or OMe; or Z^1 and Z^2 together are a fused 1,3-dioxolane ring.

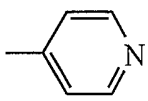
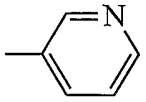
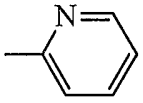
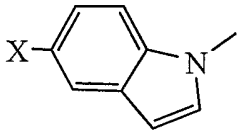
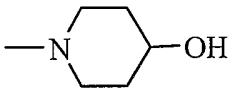
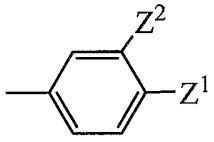
In another aspect, the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:


(Vb), 
(VIb); or 
(VIIb);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

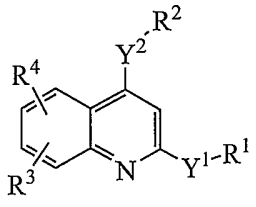
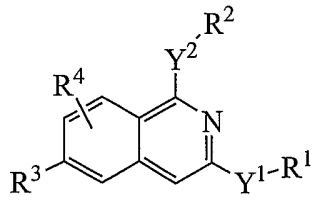
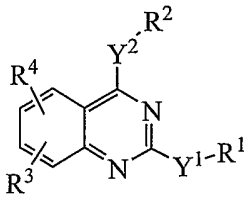
Y^1 and Y^2 are selected independently from $-(CH_2)n-$ wherein n is 0 or 1, >NH, or >O;

R^1 and R^2 are selected independently from: 
, wherein X is selected from H, F, Cl, Br, I, OMe, OEt, or OPh in the 2-, 3-, or 4-position; 
, wherein E is selected from O, S, NH, or NMe; 
, wherein R and R'

are selected independently from Me, Et, Pr, Bu, or Ph;  ;  ;  ;  , wherein X is selected from H or Cl;  ; when Y^1 or Y^2 is -(CH_2)n- and n is 0, NR_2, wherein R is selected from Me or Et; or  , wherein Z^1 and Z^2 are selected independently from H, F, Cl, Br, I, Me, Et, Pr, Bu, Ph, OH, OMe, OEt, OPr, OBu, OPh, SMe, SEt, SPr, SBu, SPh, SO_2Me, SO_2Et, SO_2Pr, SO_2Bu, or SO_2Ph; or Z^1 and Z^2 together are a fused 1,3-dioxolane ring; and

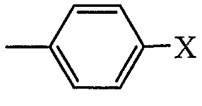
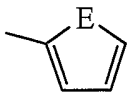
R^3 and R^4 are selected independently from H, Me, Et, Pr, or Bu.

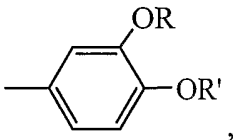
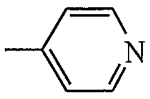
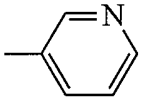
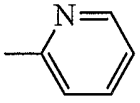
In still a further aspect, this invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

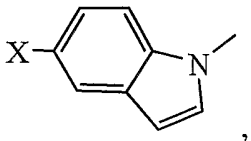
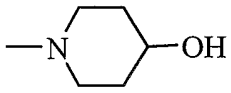
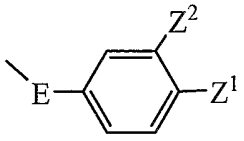
 **(Vc)**,  **(VIc)**; or 

(VIIc);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

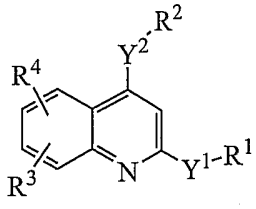
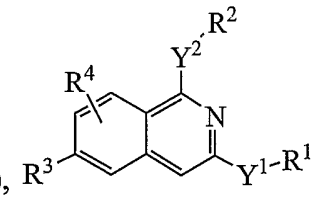
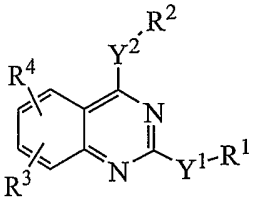
Y^1R^1 is selected from:  , wherein X is selected from H, F, Cl, Br, I, OMe, OEt, or OPh;  , wherein E is selected from O, S, NH, or NMe;


, wherein R and R' are selected independently from Me, Et, Pr, Bu, or Ph;  ;  ; or  ;

Y^2R^2 is selected from: NR_2, wherein R is selected from Me or Et;  , wherein X is selected from H or Cl;  ; or  , wherein E is selected from >O or >NH; Z^1 and Z^2 are selected independently from H, F, Cl, Br, I, Me, Et, Pr, Bu, Ph, OH, OMe, OEt, OPr, OBu, OPh, SMe, SEt, SPr, SBu, SPh, SO_2Me, SO_2Et, SO_2Pr, SO_2Bu, or SO_2Ph; or Z^1 and Z^2 together are a fused 1,3-dioxolane ring; and

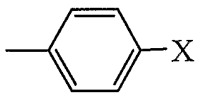
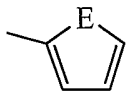
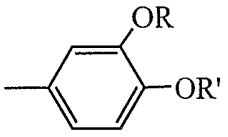
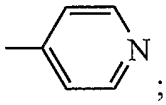
R^3 and R^4 are selected independently from H, Me, Et, Pr, or Bu.

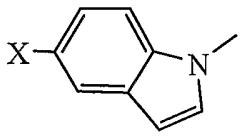
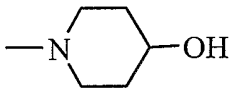
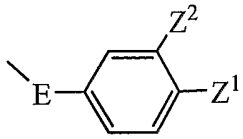
In yet another aspect, this invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

 **(Vd)**,  **(VId)**; or 

(VIId);

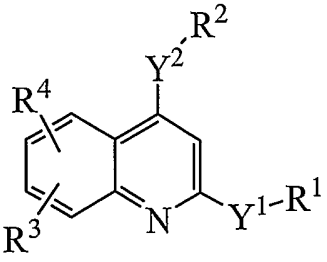
or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is selected from:  , wherein X is selected from H, F, Cl, Br, I, OMe, or OEt;  , wherein E is selected from O of NH;  , wherein R and R' are selected independently from Me or Et; or  ;

Y^2R^2 is selected from: NR_2, wherein R is selected from Me or Et;  , wherein X is selected from H or Cl;  ; or  , wherein E is selected from >O or >NH; Z^1 is selected from H, OH, OMe, SMe, or SO_2Me; Z^2 is selected from H, F, Cl, Me, or OMe; or Z^1 and Z^2 together are a fused 1,3-dioxolane ring; and

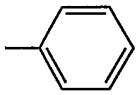
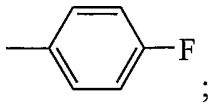
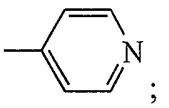
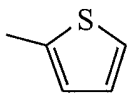
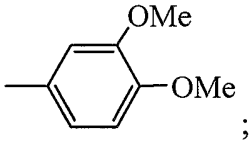
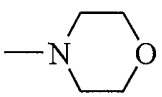
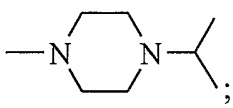
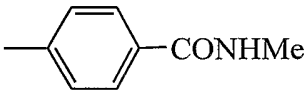
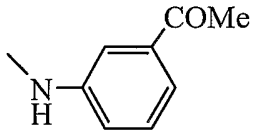
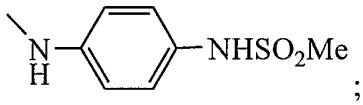
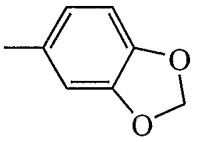
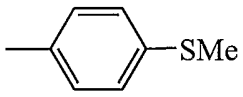
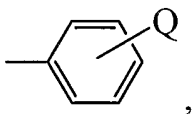
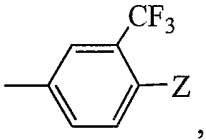
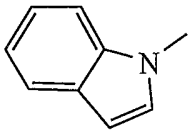
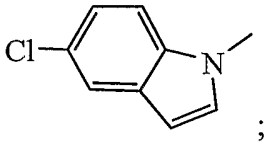
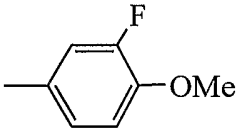
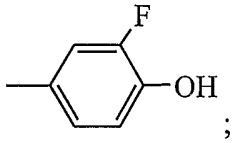
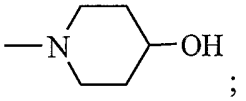
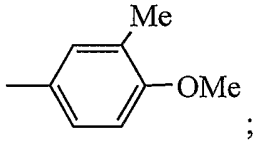
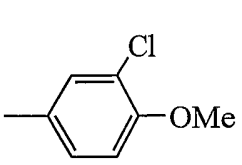
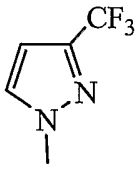
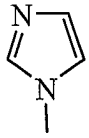
R^3 and R^4 are selected independently from H or Me.

Another aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

 **(Ve);**

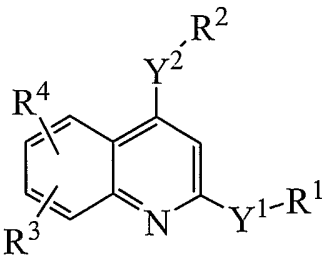
or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 and Y^2 are selected independently from -(CH_2)n- wherein n is 0 or 1, >NH, or >O;

R^1 and R^2 are selected independently from:  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  , wherein Q is 2-OCF_3, 2-SO_2Me, 2-SO_2NH_2, 3-OCF_3, 3-SO_2Me, 3-SO_2NH_2, 4-OCF_3, 4-SO_2Me, or 4-SO_2NH_2;  , wherein Z is F, Cl, Br, or I;  ;  ;  ;  ;  ;  ;  ;  ; or  ; and

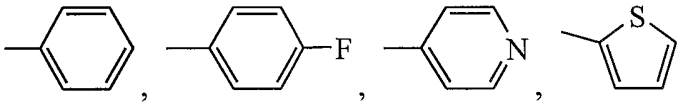
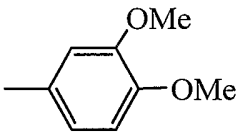
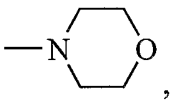
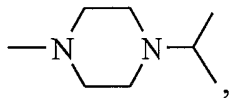
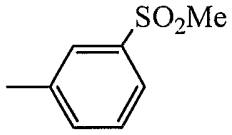
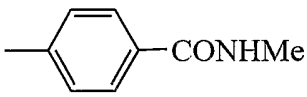
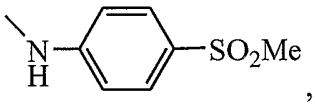
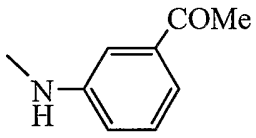
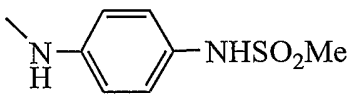
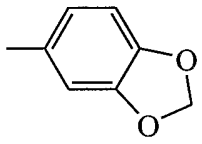
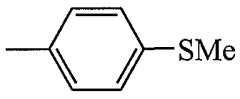
R^3 and R^4 are H.

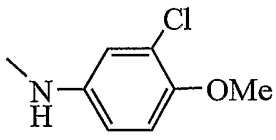
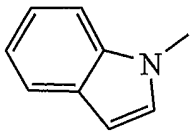
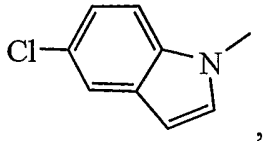
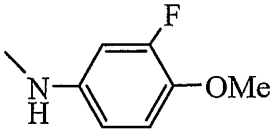
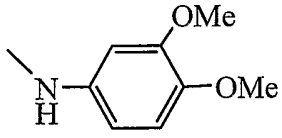
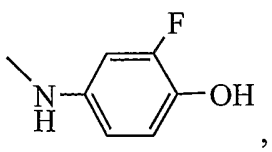
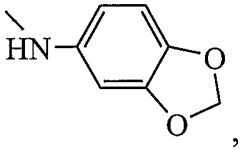
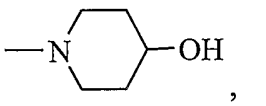
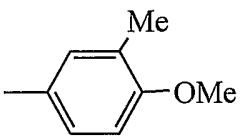
In yet another aspect, the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

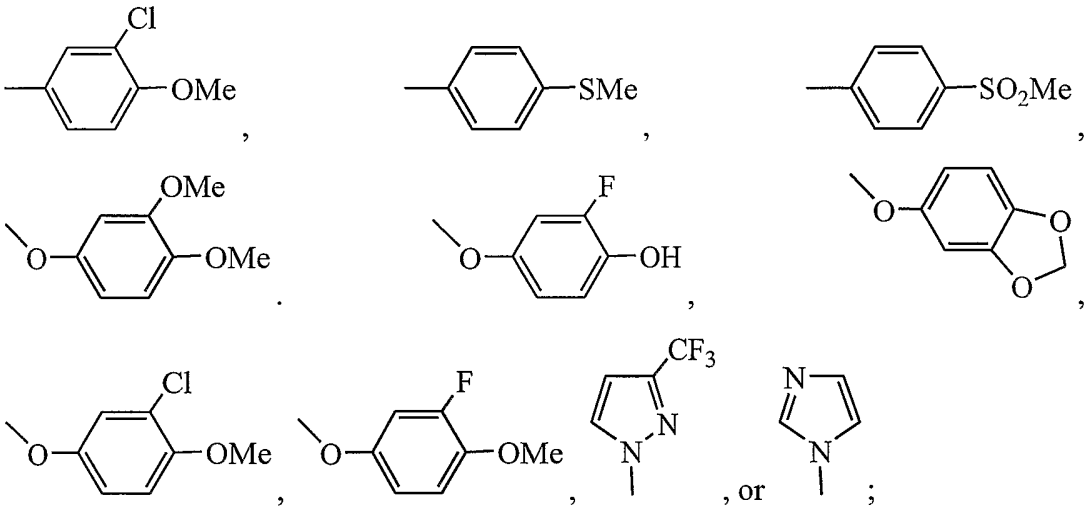


(Vf);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is selected from  , , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

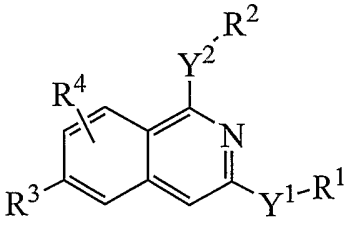
Y^2R^2 is selected from NMe_2,  ,  ,  ,  ,  ,  ,  ,  , 



R^3 is H; and

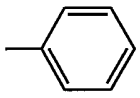
R^4 is H.

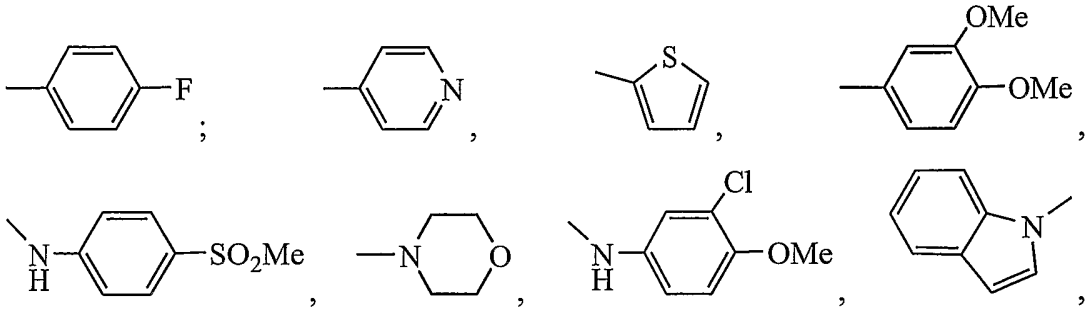
In still another aspect, the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

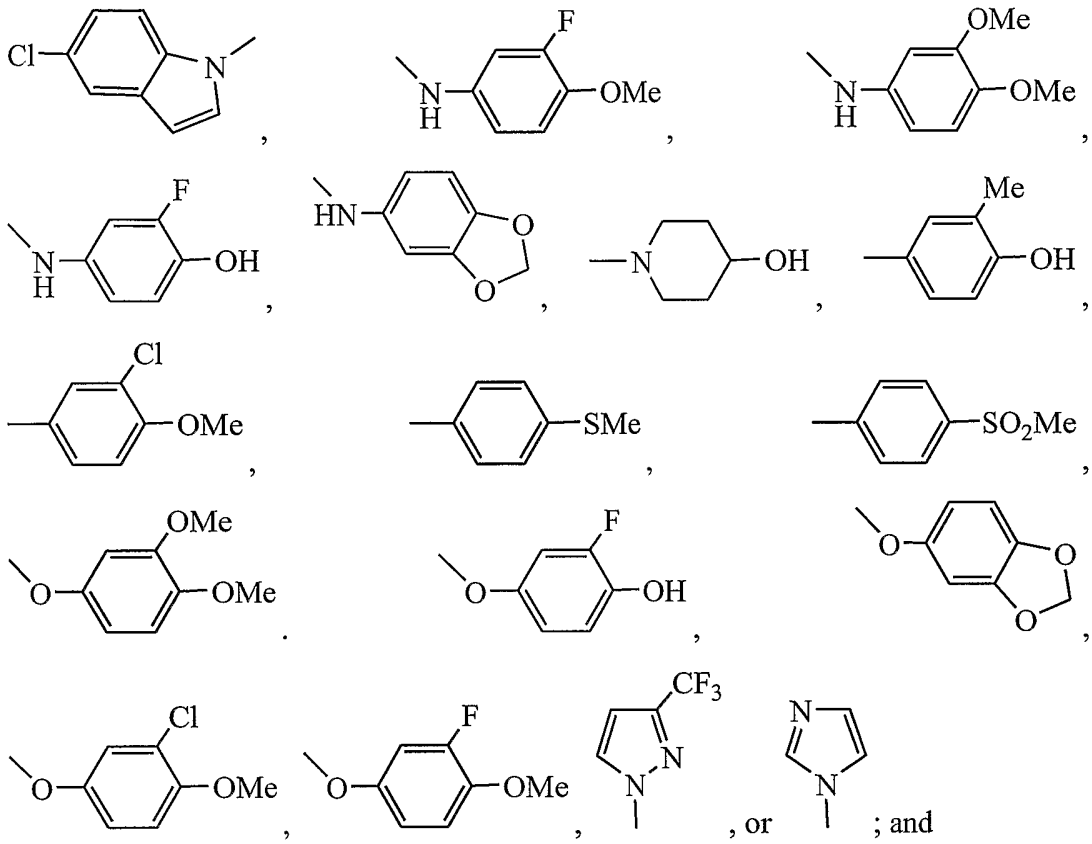


(VIe);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

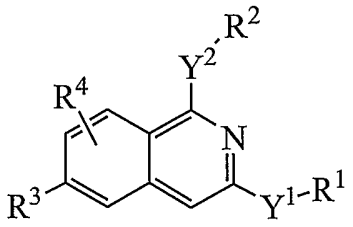
Y^1R^1 and Y^2R^2 are selected independently from NMe_2,  ,





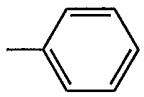
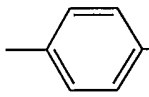
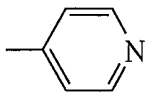
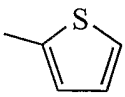
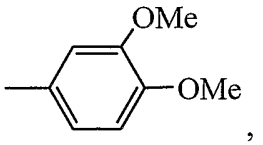
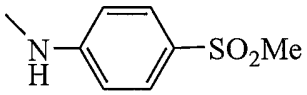
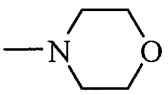
R^3 and R^4 are selected independently from H or Me.

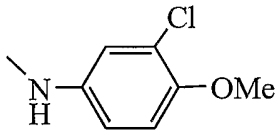
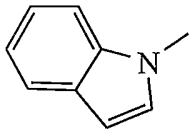
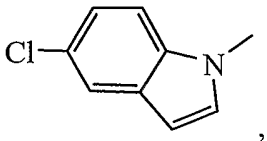
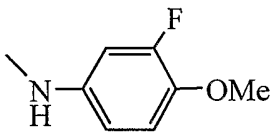
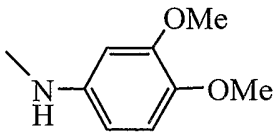
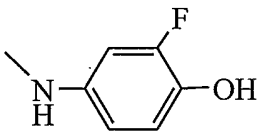
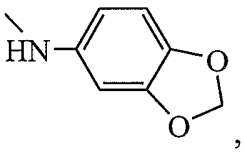
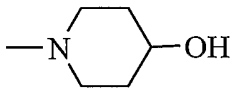
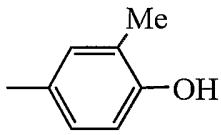
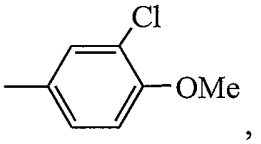
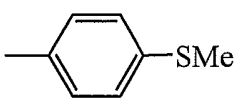
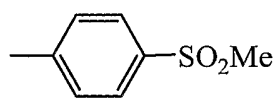
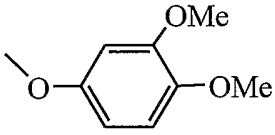
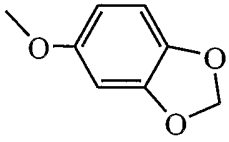
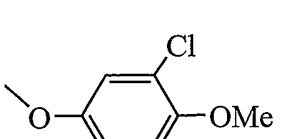
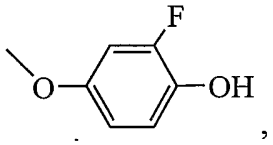
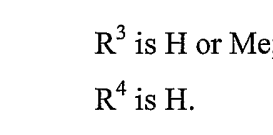
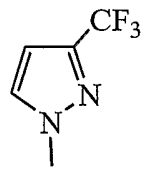
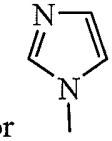
In still another aspect, this invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:



(VIf);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

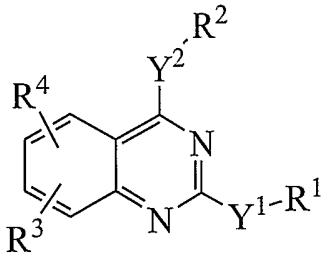
Y^1R^1 is selected from  ,  ,  ,  ,  ,  , or  ;

Y^2R^2 is selected from NMe_2,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,  , ,  ,  , or ;

R^3 is H or Me; and

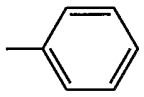
R^4 is H.

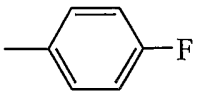
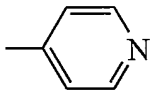
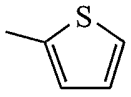
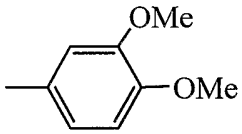
A further aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

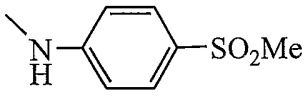
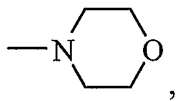
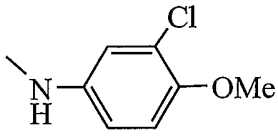
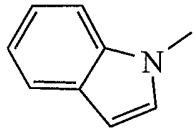


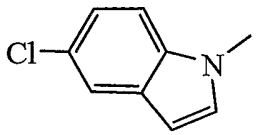
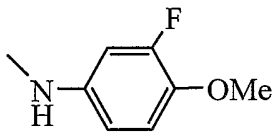
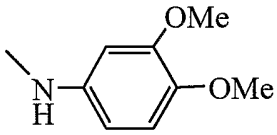
(VIIe);

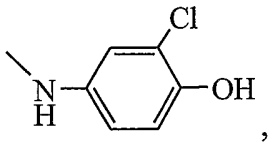
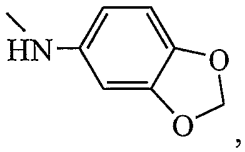
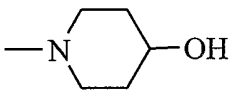
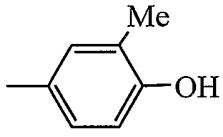
or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

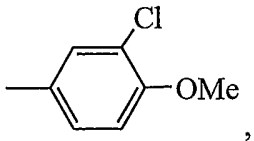
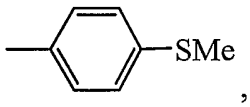
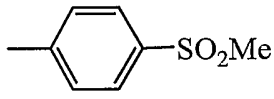
Y^1R^1 and Y^2R^2 are selected independently from NMe_2,  ,

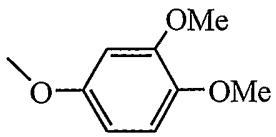
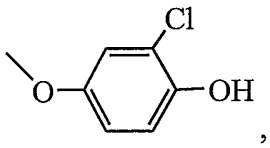
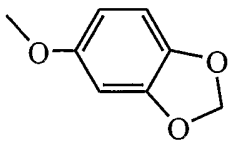
 ;
 ,
 ,
 ,

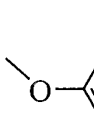
 ,
 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,
 ,

 ,
 ,
 ,

 .
 ,
 ,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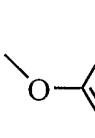
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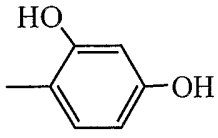
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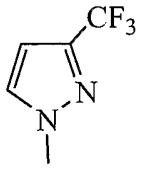
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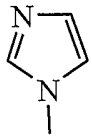
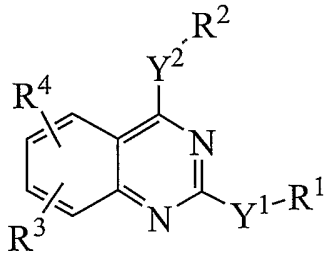
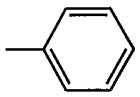
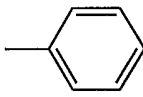

; and

R^3 and R^4 are selected independently from H or Me.

In still a further aspect, the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:


(VIIf);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is selected from

,

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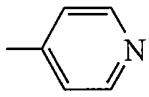
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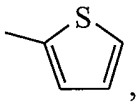
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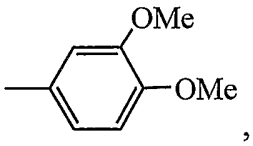
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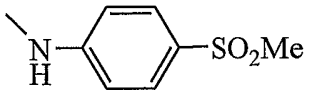
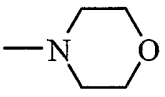
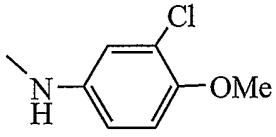

, or

;

Y^2R^2 is selected from NMe_2,

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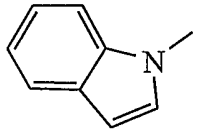
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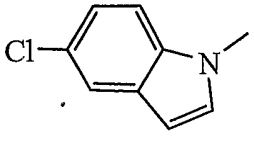
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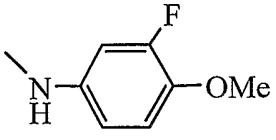
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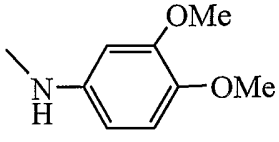
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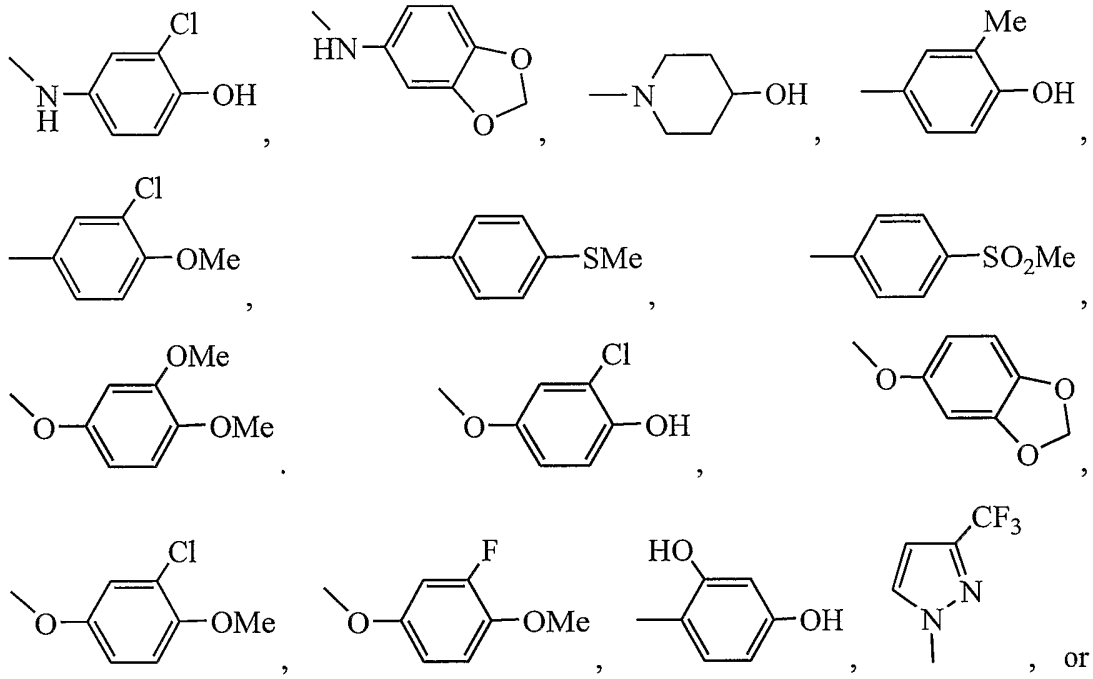
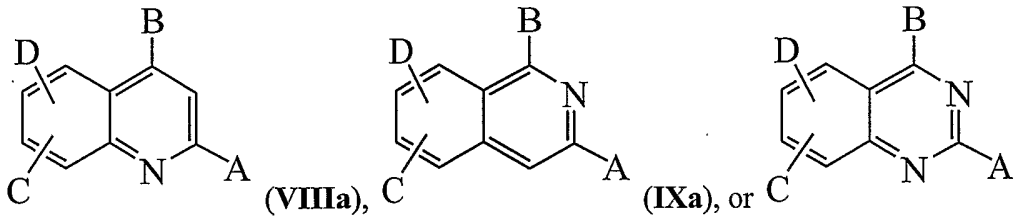


;

R^3 is H; and

R^4 is H.

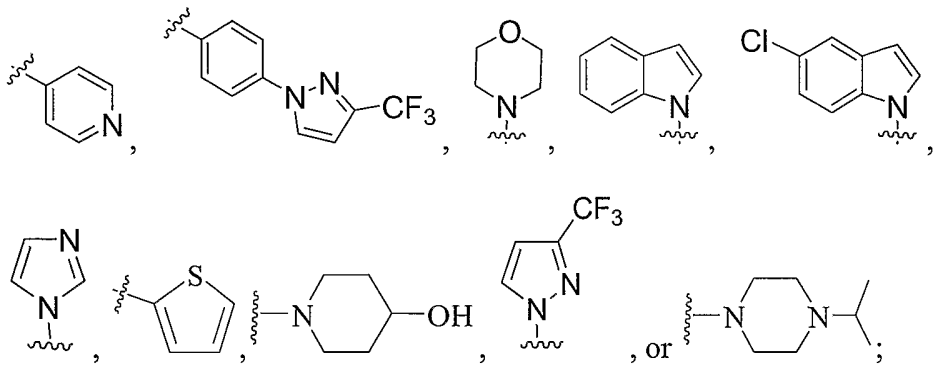
An additional aspect of the present invention provides heterocyclic compounds, and compositions comprising the heterocyclic compounds, wherein the compounds have the following formula:

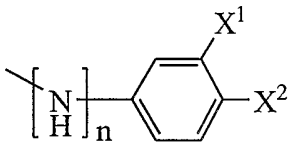
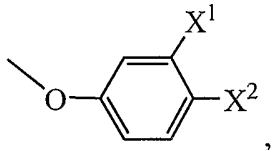


(VIIIa), **(IXa)**, or **(Xa)**;

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

A and B are selected independently from A1, A2, or A3, wherein:

A1 

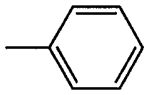
A2 is  wherein n is 0 or 1, or  ,

wherein:

X^1 is H, F, Cl, OH, OMe, Me, SO_2Me, or C(O)Me; and

X^2 is H, F, Cl, OH, OMe, SMe, Me, CF_3, OCF_3, SO_2Me, SO_2NH_2, SO_2NHMe, SO_2NMe_2, $C(O)NH_2$, C(O)NHMe, $C(O)NMe_2$, $NHSO_2Me$, or X^1 and X^2 form a fused 1,3-dioxolane ring; and

A3 is NMe_2 or NEt_2; and

C and D are selected independently from H, Me, Et, *n*-Pr, or  .

Further to this aspect of the invention and to the formulas **(VIIIa)**, **(IXa)**, or **(Xa)** presented immediately above, the following substituents of the formulas **(VIIIa)**, **(IXa)**, or **(Xa)** can be selected as indicated, while unspecified substitutents are selected as above:

1) A can be selected from A1, A2, or A3, and B can be selected from A1;

2) A can be selected from A1, A2, or A3, and B can be selected from A2;

3) A can be selected from A1, A2, or A3, and B can be selected from A3;

4) A can be selected from A1 or A2, and B can be selected from A1;

5) A can be selected from A1 or A2, and B can be selected from A2;

6) A can be selected from A1 or A2, and B can be selected from A3;

7) A can be selected from A1 and B can be selected from A1;

8) A can be selected from A1 and B can be selected from A2;

9) A can be selected from A1 and B can be selected from A3;

10) A can be selected from A2 and B can be selected from A1;

11) A can be selected from A2 and B can be selected from A2;

12) A can be selected from A2 and B can be selected from A3;

13) A can be selected from A3 and B can be selected from A1;

14) A can be selected from A3 and B can be selected from A2; or

15) A can be selected from A3 and B can be selected from A3.

Additionally, and further to this aspect of the invention and to the formulas **(VIIIa)**, **(IXa)**, or **(Xa)** presented above, the following substituents of the formulas **(VIIIa)**, **(IXa)**, or **(Xa)** can be selected as indicated, while unspecified substitutents are selected as above:

1) B can be selected from A1, A2, or A3, and A can be selected from A1;

2) B can be selected from A1, A2, or A3, and A can be selected from A2;

3) B can be selected from A1, A2, or A3, and A can be selected from A3;

4) B can be selected from A1 or A2, and A can be selected from A1;

5) B can be selected from A1 or A2, and A can be selected from A2;

6) B can be selected from A1 or A2, and A can be selected from A3;

7) B can be selected from A1 and A can be selected from A1;

8) B can be selected from A1 and A can be selected from A2;

9) B can be selected from A1 and A can be selected from A3;

10) B can be selected from A2 and A can be selected from A1;

11) B can be selected from A2 and A can be selected from A2;

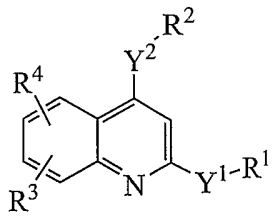
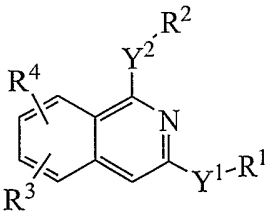
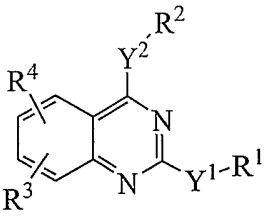
12) B can be selected from A2 and A can be selected from A3;

13) B can be selected from A3 and A can be selected from A1;

14) B can be selected from A3 and A can be selected from A2; or

15) B can be selected from A3 and A can be selected from A3.

According to another aspect of this invention, and consistent with the definitions provided herein, the present invention also provides for compounds of the following general structures:


(**XI**),

(**XII**), or

(**XIII**);

or a salt, including a pharmaceutically acceptable or a non-pharmaceutically acceptable salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein within each structure, the substituents Y^1, R^1, Y^2, R^2, R^3 and R^4 can be selected according to the following listings, wherein each substituent is defined in the following table.

The substituent Y^1 and Y^2 can be selected independently from Y^A, Y^B, Y^C, Y^D, Y^E, Y^F, Y^G, Y^H, Y^I, or Y^J.

The substituent R^1 can be selected independently from R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{1E}, R^{1F}, R^{1G1}, R^{1G2}, R^{1G3}, R^{1G4}, R^{1G5}, R^{1G6}, R^{1H1}, R^{1H2}, R^{1H3}, R^{1I}, R^{1J}, R^{1K}, R^{1L}, R^{1M}, R^{1N}, R^{1O}, R^{1P}, or R^{1Q}.

The substituent R^2 can be selected independently from R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{2E}, R^{2F}, R^{2G1}, R^{2G2}, R^{2G3}, R^{2G4}, R^{2G5}, R^{2G6}, R^{2H1}, R^{2H2}, R^{2H3}, R^{2I}, R^{2J}, R^{2K}, R^{2L}, R^{2M}, R^{2N}, R^{2O}, R^{2P}, or R^{2Q}.

Alternatively, the moieties Y^1R^1 and Y^2R^2 can be selected independently from YR^A, YR^B, YR^C, YR^D, YR^E, YR^F, YR^G, YR^H, YR^I, YR^J, YR^K, or YR^L, as defined herein.

The substituent R^3 can be selected independently from R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{3E}, R^{3F}, R^{3G}, R^{3H}, R^{3I}, R^{3J}, R^{3K}, R^{3L}, R^{3M}, R^{3N}, R^{3O}, R^{3P1}, R^{3P2}, R^{3P3}, R^{3P4}, R^{3P5}, R^{3P6}, R^{3Q1}, R^{3Q2}, R^{3Q3}, R^{3R}, R^{3S}, R^{3T}, R^{3U}, or R^{3V}.

The substituent R^4 can be selected independently from R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{4E}, R^{4F}, R^{4G}, R^{4H}, R^{4I}, R^{4J}, R^{4K}, R^{4L}, R^{4M}, R^{4N}, R^{4O}, R^{4P1}, R^{4P2}, R^{4P3}, R^{4P4}, R^{4P5}, R^{4P6}, R^{4Q1}, R^{4Q2}, R^{4Q3}, R^{4R}, R^{4S}, R^{4T}, R^{4U}, or R^{4V}.

The substituents recited above are defined as follows, consistent with the definitions provided herein.

Table 1. Substituent abbreviations.

Y^A	$>NR^5$, wherein R^5 is defined below
Y^B	$-(CH_2)n-$, n is 0 to 3
Y^C	$-(CH_2)p(CH=CH)(CH_2)q-$, p and q are independently 0 to 3
Y^D	$>CR^5R^6$, wherein R^5 and R^6 are defined below
Y^E	$-(CH_2)p(C\equiv C)(CH_2)q-$, p and q are independently 0 to 3
Y^F	>O
Y^G	>CO
Y^H	>S
Y^I	>SO
Y^J	$>SO_2$
YR^A	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms
YR^B	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms, further comprising >O in the ring
YR^C	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms, further comprising >N- in the ring
YR^D	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms, further comprising >S in the ring
YR^E	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms, further comprising $>NR^6$ in the ring, wherein R^6 is defined below
YR^F	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms, further comprising $>SO_2$ in the ring
YR^G	saturated or unsaturated carbocyclic or N-heterocyclic ring having up to 12 carbon atoms, further comprising >CO in the ring
YR^H	substituted or an unsubstituted morpholinyl
YR^I	substituted or an unsubstituted piperazinyl
YR^J	substituted or an unsubstituted thiomorpholinyl
YR^K	substituted or an unsubstituted pyrrolidinyl
YR^L	substituted or an unsubstituted piperidinyl
R^{1A}, R^{2A}	Alkyl having up to 12 carbon atoms
R^{1B}, R^{2B}	Aryl having up to 12 carbon atoms
R^{1C}, R^{2C}	Alkoxyalkyl having up to 12 carbon atoms
R^{1D}, R^{2D}	Cycloalky having up to 12 carbon atoms
R^{1E}, R^{2E}	$-COR^5$ having up to 12 carbon atoms, wherein R^5 is defined below
R^{1F}, R^{2F}	Aralkyl having up to 12 carbon atoms
R^{1G1}, R^{2G1}	Heterocyclyl having up to 12 carbon atoms, comprising >O
R^{1G2}, R^{2G2}	Heterocyclyl having up to 12 carbon atoms, comprising >N-

R^{1G3}, R^{2G3}	Heterocyclyl having up to 12 carbon atoms, comprising >S
R^{1G4}, R^{2G4}	Heterocyclyl having up to 12 carbon atoms, comprising >NR^6, wherein R^6 is defined below
R^{1G5}, R^{2G5}	Heterocyclyl having up to 12 carbon atoms, comprising >SO_2
R^{1G6}, R^{2G6}	Heterocyclyl having up to 12 carbon atoms, comprising >CO
R^{1H1}, R^{2H1}	Heteroaryl having up to 12 carbon atoms, comprising >O
R^{1H2}, R^{2H2}	Heteroaryl having up to 12 carbon atoms, comprising >N- or >NR^6, wherein R^6 is defined below
R^{1H3}, R^{2H3}	Heteroaryl having up to 12 carbon atoms, comprising >S
R^{1I}, R^{2I}	Hydrogen
R^{1J}, R^{2J}	Halogen
R^{1K}, R^{2K}	Cyano
R^{1L}, R^{2L}	Hydroxyl
R^{1M}, R^{2M}	Alkoxy having up to 12 carbon atoms
R^{1N}, R^{2N}	Alkenyl having up to 12 carbon atoms
R^{1O}, R^{2O}	Alkynyl having up to 12 carbon atoms
R^{1P}, R^{2P}	-CO_2R^5 having up to 12 carbon atoms, wherein R^5 is defined below
R^{1Q}, R^{2Q}	-COR^5 having up to 12 carbon atoms, wherein R^5 is defined below
R^{3A}, R^{4A}	Alkyl having up to 12 carbon atoms
R^{3B}, R^{4B}	Alkenyl having up to 12 carbon atoms
R^{3C}, R^{4C}	Alkynyl having up to 12 carbon atoms
R^{3D}, R^{4D}	Alkoxy having up to 12 carbon atoms
R^{3E}, R^{4E}	Cycloalkyl having up to 12 carbon atoms
R^{3F}, R^{4F}	Haloalkyl having up to 12 carbon atoms
R^{3G}, R^{4G}	Haloalkoxy having up to 12 carbon atoms
R^{3H}, R^{4H}	Alkylthio having up to 12 carbon atoms
R^{3I}, R^{4I}	Alkylsulfonyl having up to 12 carbon atoms
R^{3J}, R^{4J}	Aryl having up to 12 carbon atoms
R^{3K}, R^{4K}	-CO_2R^5 having up to 12 carbon atoms, wherein R^5 is defined below
R^{3L}, R^{4L}	-COR^5 having up to 12 carbon atoms, wherein R^5 is defined below
R^{3M}, R^{4M}	-NR^5R^6 having up to 12 carbon atoms, wherein R^5 and R^6 are defined below
R^{3N}, R^{4N}	-$SO_2NR^5R^6$ having up to 12 carbon atoms, wherein R^5 and R^6 are defined below
R^{3O}, R^{4O}	-SO_3R^5 having up to 12 carbon atoms, wherein R^5 is defined below
R^{3P1}, R^{4P1}	Heterocyclyl having up to 12 carbon atoms, comprising >O
R^{3P2}, R^{4P2}	Heterocyclyl having up to 12 carbon atoms, comprising >N-
R^{3P3}, R^{4P3}	Heterocyclyl having up to 12 carbon atoms, comprising >S

R^{3P4}, R^{4P4}	Heterocyclyl having up to 12 carbon atoms, comprising >NR^6, wherein R^6 is defined below
R^{3P5}, R^{4P5}	Heterocyclyl having up to 12 carbon atoms, comprising >SO_2
R^{3P6}, R^{4P6}	Heterocyclyl having up to 12 carbon atoms, comprising >CO
R^{3Q1}, R^{4Q1}	Heteroaryl having up to 12 carbon atoms, comprising >O
R^{3Q2}, R^{4Q2}	Heteroaryl having up to 12 carbon atoms, comprising >N- or >NR^6, wherein R^6 is defined below
R^{3Q3}, R^{4Q3}	Heteroaryl having up to 12 carbon atoms, comprising >S
R^{3R}, R^{4R}	Hydrogen
R^{3S}, R^{4S}	Halogen
R^{3T}, R^{4T}	Hydroxyl
R^{3U}, R^{4U}	Cyano
R^{3V}, R^{4V}	Y^1R^1, independent of the selection of Y^1R^1
R^5	R^{5A} R^{5B}, R^{5C}, R^{5D1}, R^{5D2}, R^{5D3}, R^{5E}, R^{5F1}, R^{5F2}, R^{5F3}, R^{5F4}, R^{5F5}, R^{5F6}, or R^{5G}
R^6	R^{6A} R^{6B}, R^{6C}, R^{6D1}, R^{6D2}, R^{6D3}, R^{6E}, R^{6F1}, R^{6F2}, R^{6F3}, R^{6F4}, R^{6F5}, R^{6F6}, or R^{6G}
R^{5A}, R^{6A}	Alkyl having up to 12 carbon atoms
R^{5B}, R^{6B}	Aryl having up to 12 carbon atoms
R^{5C}, R^{6C}	Alkoxyalkyl having up to 12 carbon atoms
R^{5D1}, R^{6D1}	Heteroaryl having up to 12 carbon atoms, comprising >O
R^{5D2}, R^{6D2}	Heteroaryl having up to 12 carbon atoms, comprising >N- or >NR^6, wherein R^6 is defined below
R^{5D3}, R^{6D3}	Heteroaryl having up to 12 carbon atoms, comprising >S
R^{5E}, R^{6E}	Cycloalkyl having up to 12 carbon atoms
R^{5F1}, R^{6F1}	Heterocyclyl having up to 12 carbon atoms, comprising >O
R^{5F2}, R^{6F2}	Heterocyclyl having up to 12 carbon atoms, comprising >N-
R^{5F3}, R^{6F3}	Heterocyclyl having up to 12 carbon atoms, comprising >S
R^{5F4}, R^{6F4}	Heterocyclyl having up to 12 carbon atoms, comprising >NR^6, wherein R^6 and R^6 is defined above
R^{5F5}, R^{6F5}	Heterocyclyl having up to 12 carbon atoms, comprising >SO_2
R^{5F6}, R^{6F6}	Heterocyclyl having up to 12 carbon atoms, comprising >CO
R^{5G}, R^{6G}	Hydrogen

In these selections, unless otherwise indicated, the number of carbon atoms on the substituents refers to the carbon atoms on the base chemical moiety, and does not include the carbon atoms in any optional substituent. Again, unless otherwise

indicated, any substituents are limited in size by the carbon atoms listed in the definitions of the substitutents.

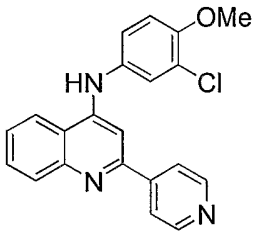
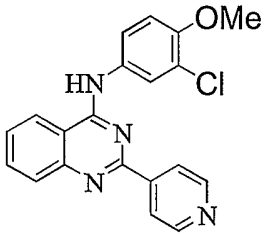
In these selections, the following features are applicable. Any carbocyclic ring, N-heterocyclic ring, morpholinyl, piperazinyl, thiomorpholinyl, pyrrolidinyl, or piperidinyl can be optionally substituted with at least one hydroxyl, halogen, alkyl, alkoxy, haloalkyl, cycloalkyl, aryl, or heteroaryl any of which having up to 6 carbon atoms. Further any when a piperazinyl moiety is present in the substituted heterocyclic compound, the piperazine nitrogen is optionally substituted by an alkyl, a cycloalkyl, an acyl, a haloalkyl, an alkoxyalkyl, SO_2R^7, $SO_2NR^7_2$, or CO_2R^7, wherein R^7 is independently selected from: a) an alkyl or an aryl having up to 8 carbon atoms; or b) hydrogen.

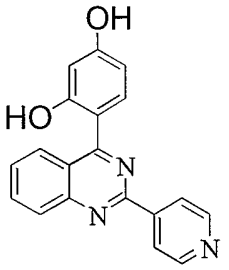
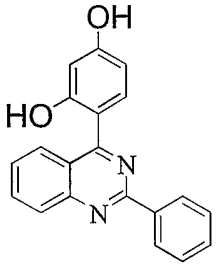
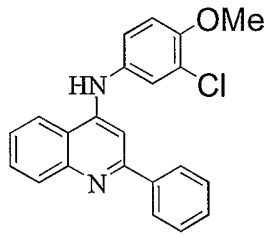
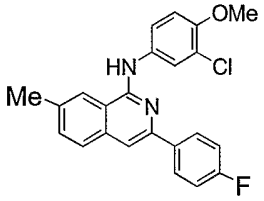
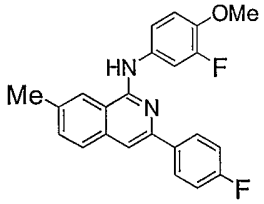
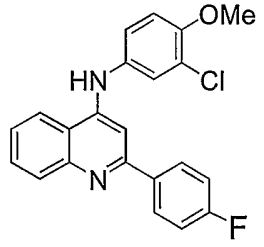
Any of the R^1, R^2, R^5, or R^6 moieties that do not constitute hydrogen, halogen, cyano, or hydroxyl (for example, R^{1A} through R^{1H}, R^{1M} through R^{1Q}, R^{2A} through R^{2H}, R^{2M} through R^{2Q}, R^{3A} through R^{3Q} and R^{3V}, R^{4A} through R^{4Q} and R^{4V}, R^{5A} through R^{5F}, and R^{6A} through R^{6F}) can be optionally substituted with at least one group independently selected from: 1) alkyl; alkoxy; alkylthio; haloalkyl; cycloalkyls; aryl; heterocyclyl or heteroaryl comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO; haloalkoxy; $-OCH_2O-$; $-OCOR^9$; $N(R^8)_2$; $-COR^9$; $-CON(R^8)_2$; $-(CH_2)_bCO_2R^8$ wherein b is an integer from 0 to 3; $-OCO(CH_2)_b-CO_2R^{10}$ wherein b is an integer from 0 to 3; $-SO_2R^9$; $-NHSO_2R^9$; or $-SO_2N(R^8)_2$; any of which having up to 12 carbon atoms; or 2) hydrogen, halogen, hydroxyl, or cyano. In these groups, R^8, in each occurrence, is independently: 1) an alkyl; a haloalkyl; a heterocyclyl or heteroaryl comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO; or an aryl having up to 6 carbon atoms; or 2) hydrogen. Further, in these moieties, R^9, in each occurrence, is independently an alkyl; a haloalkyl; an aryl; or a heterocyclyl or heteroaryl comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO; having up to 8 carbon atoms; wherein R^9 is optionally substituted with: 1) an alkyl, an alkoxy, a carboxylic acid, or a carboxylic acid ester, any of which having up to 8 carbon atoms; 2) halogen; or 3) hydroxyl.

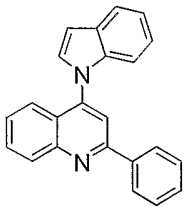
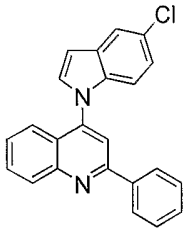
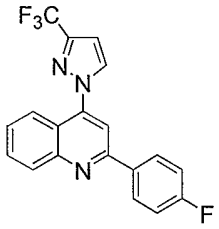
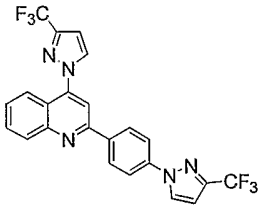
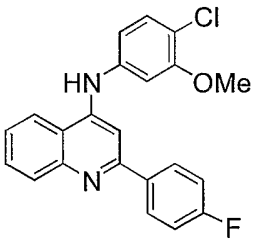
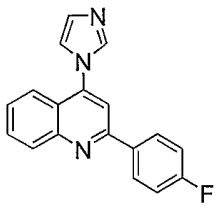
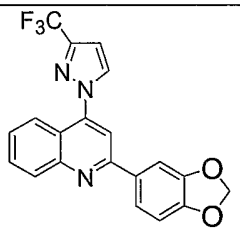
Any of the R^3 or R^4 moieties that do not constitute hydrogen, halogen, cyano, or hydroxyl can be optionally substituted with at least one group independently selected from: 1) alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, alkenyl, alkynyl, $-COR^{10}$, $-CO_2R^{10}$, $-CON(R^{10})_2$, $-SO_2R^{10}$, $-SO_2N(R^{10})_2$, or $-N(R^{10})_2$, any of which having up to 12 carbon atoms; 2) halogen; or 3) hydroxyl; wherein R^{10}, in each occurrence, is independently: 1) an alkyl or an aryl having up to 6 carbon atoms; or 2) hydrogen.

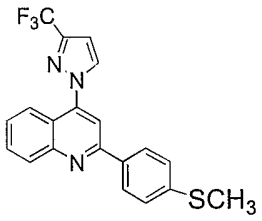
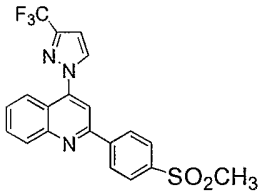
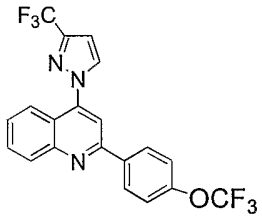
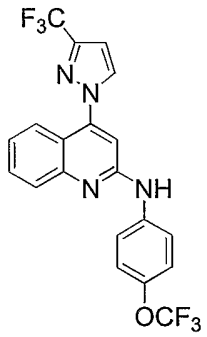
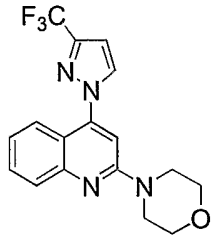
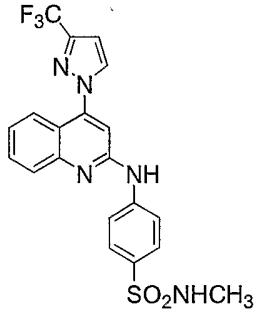
Representative compounds in accordance with the present invention are presented in the following table. Any table of specific compounds presented herein is not intended to be an exhaustive listing or exclusive of the compounds of the present invention, but rather exemplary of the heterocyclic compounds that are encompassed by this invention. Further, any listing of a compound as a salt is also intended to be inclusive of the neutral analog of that compound as well, and listing of a neutral compound is also intended to be inclusive of any salt thereof.

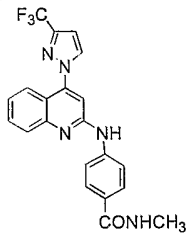
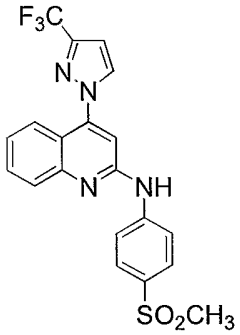
Table 2. Representative compounds in accordance with the present invention

Entry	Structure	Name
E 1		(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine
E 2		(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine

E 3		4-(2-Pyridin-4-yl-quinazolin-4-yl)-benzene-1,3-diol
E 4		4-(2-Phenyl-quinazolin-4-yl)-benzene-1,3-diol
E 5		(3-Chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine
E 6		(3-Chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine
E 7		(3-Fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine
E 8		(3-Chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine

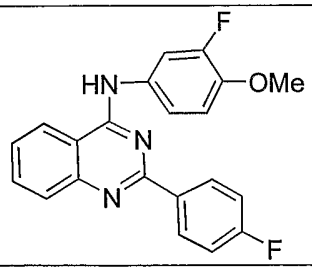
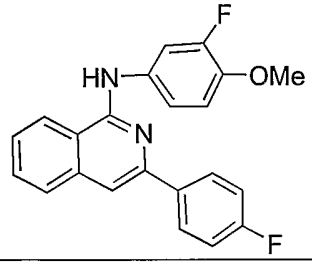
E 9		4-Indol-1-yl-2-phenyl-quinoline
E 10		4-(5-Chloro-indol-1-yl)-2-phenyl-quinoline
E 11		2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
E 12		4-(3-Trifluoromethyl-pyrazol-1-yl)-2-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-quinoline
E 13		(4-Chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
E 14		2-(4-Fluoro-phenyl)-4-imidazol-1-yl-quinoline
E 15		2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline

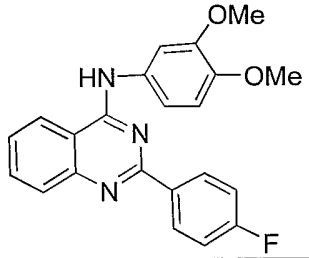
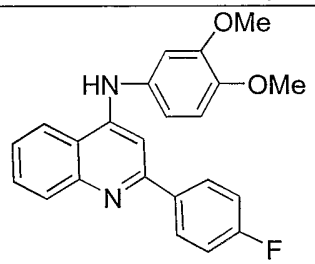
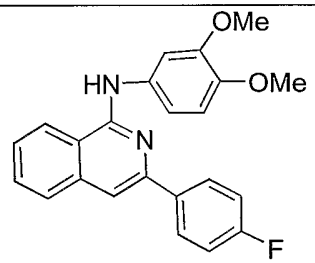
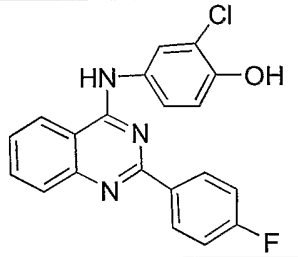
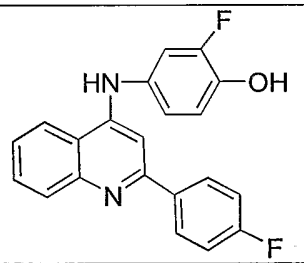
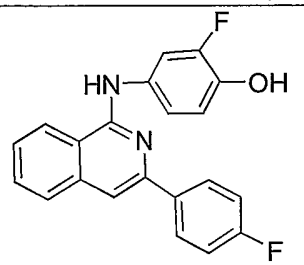
E 16		2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
E 17		2-(4-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
E 18		2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
E 19		(4-Trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine
E 20		2-Morpholin-4-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
E 21		N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide

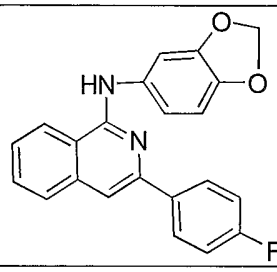
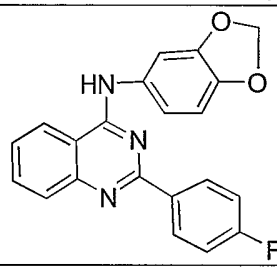
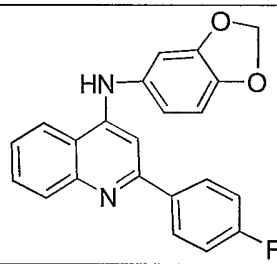
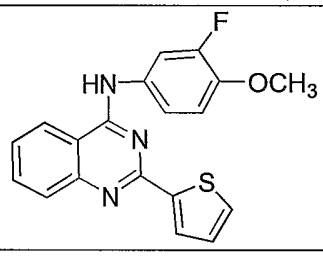
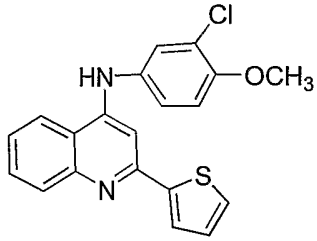
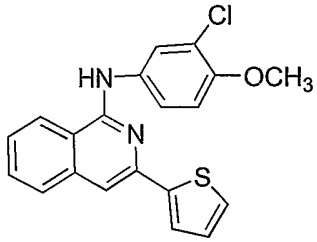
E 22		N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide
E 23		(4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine

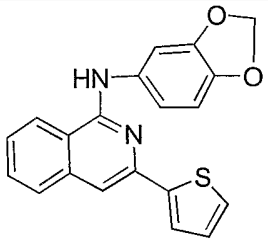
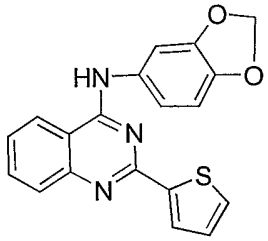
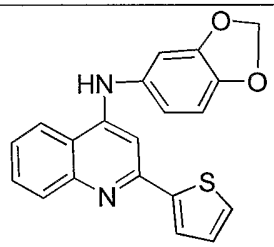
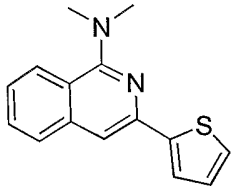
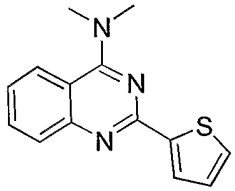
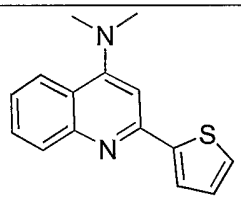
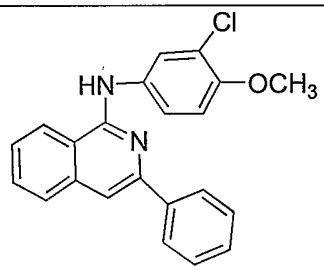
Additional representative compounds in accordance with the present invention are presented below. Again, this table is not intended to be exclusive of the compounds of the present invention, but rather exemplary of the compounds that are encompassed by this invention.

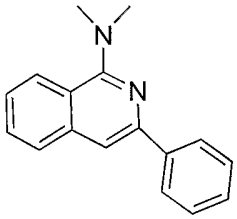
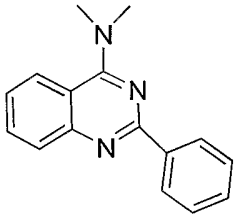
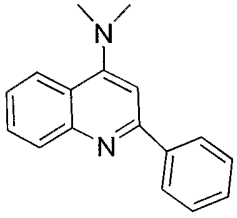
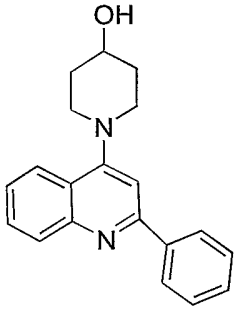
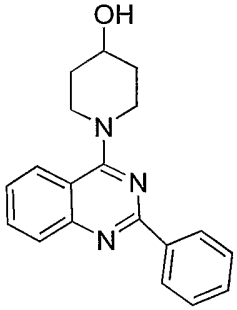
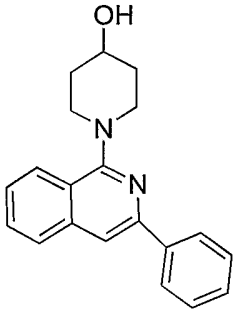
Table 3. Representative compounds in accordance with the present invention

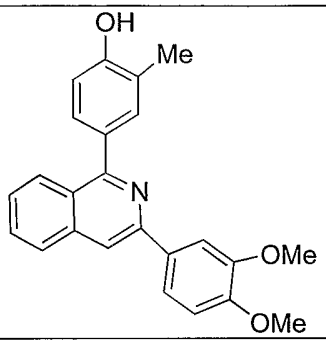
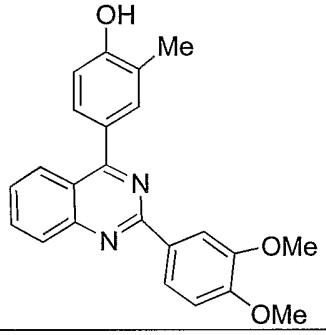
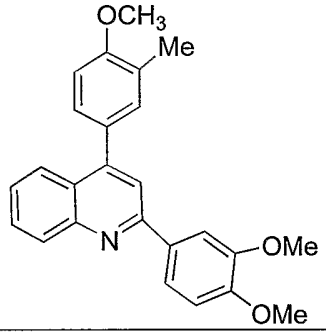
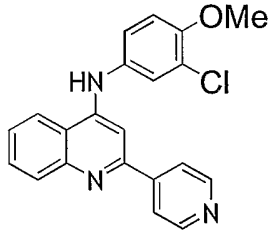
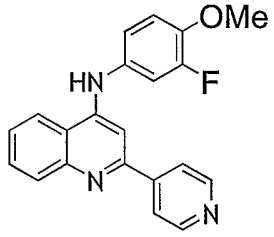
Entry	Structure	Compound Name
1.		(3-Fluoro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinazolin-4-yl]-amine
2.		(3-Fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-isoquinolin-1-yl]-amine

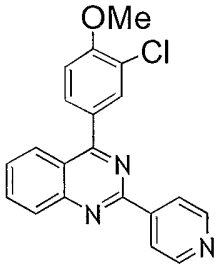
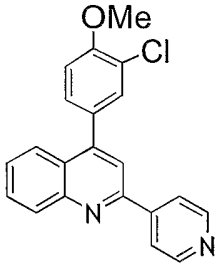
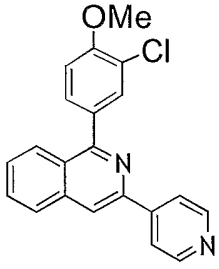
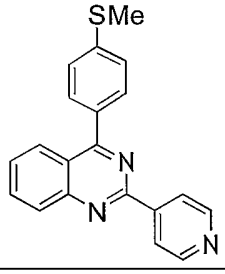
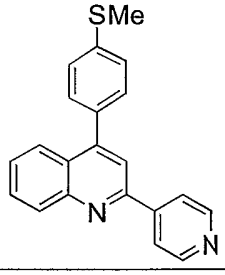
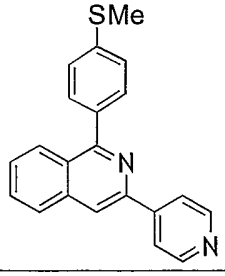
3.		(3,4-Dimethoxy-phenyl)-[2-(4-fluoro-phenyl)-quinazolin-4-yl]-amine
4.		(3,4-Dimethoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
5.		(3,4-Dimethoxy-phenyl)-[3-(4-fluoro-phenyl)-isoquinolin-1-yl]-amine
6.		2-Chloro-4-[2-(4-fluoro-phenyl)-quinazolin-4-ylamino]-phenol
7.		2-Fluoro-4-[2-(4-fluoro-phenyl)-quinolin-4-ylamino]-phenol
8.		2-Fluoro-4-[3-(4-fluoro-phenyl)-isoquinolin-1-ylamino]-phenol

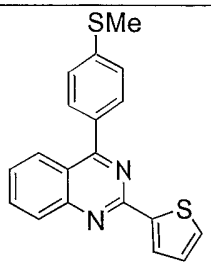
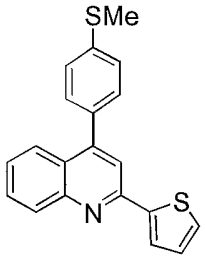
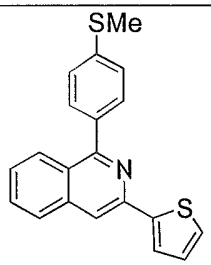
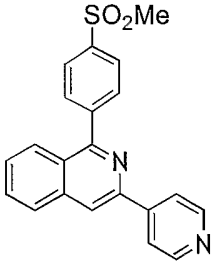
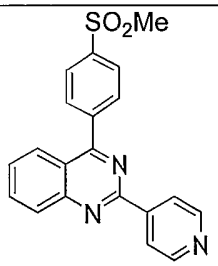
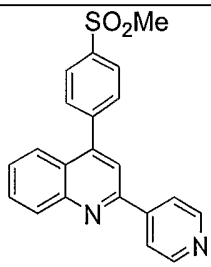
9.		Benzo[1,3]dioxol-5-yl-[3-(4-fluoro-phenyl)-isoquinolin-1-yl]-amine
10.		Benzo[1,3]dioxol-5-yl-[2-(4-fluoro-phenyl)-quinazolin-4-yl]-amine
11.		Benzo[1,3]dioxol-5-yl-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
12.		(3-Fluoro-4-methoxy-phenyl)-(2-thio phen-2-yl-quinazolin-4-yl)-amine
13.		(3-Chloro-4-methoxy-phenyl)-(2-thio phen-2-yl-quinolin-4-yl)-amine
14.		(3-Chloro-4-methoxy-phenyl)-(3-thio phen-2-yl-isoquinolin-1-yl)-amine

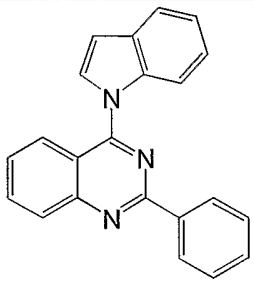
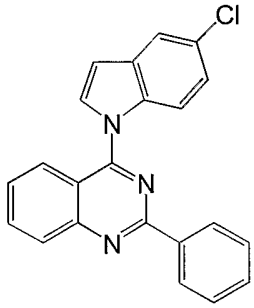
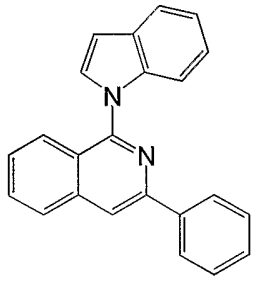
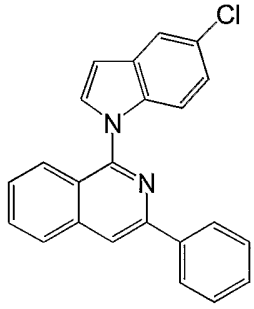
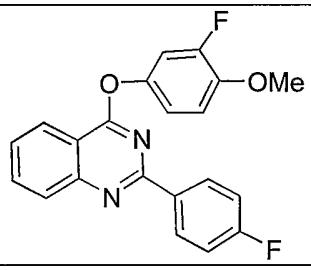
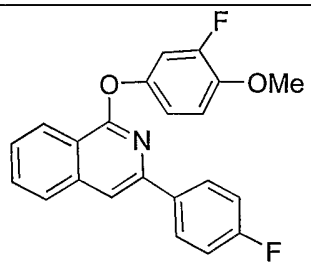
15.		Benzo[1,3]dioxol-5-yl-(3-thiophen-2 -yl-isoquinolin-1-yl)-amine
16.		Benzo[1,3]dioxol-5-yl-(2-thiophen-2 -yl-quinazolin-4-yl)-amine
17.		Benzo[1,3]dioxol-5-yl-(2-thiophen-2 -yl-quinolin-4-yl)-amine
18.		Dimethyl-(3-thiophen-2-yl-isoquinol in-1-yl)-amine
19.		Dimethyl-(2-thiophen-2-yl-quinazoli n-4-yl)-amine
20.		Dimethyl-(2-thiophen-2-yl-quinolin-4-yl)-amine
21.		(3-Chloro-4-methoxy-phenyl)-(3-phen yl-isoquinolin-1-yl)-amine

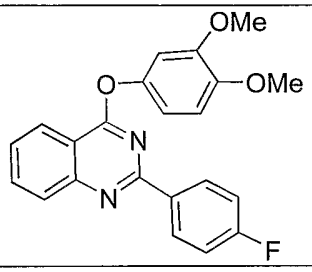
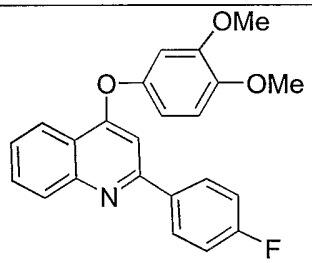
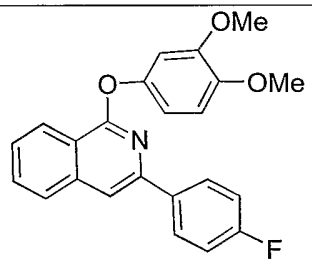
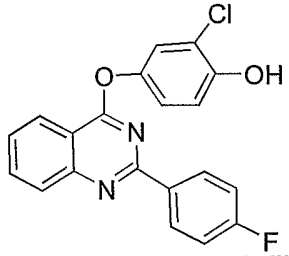
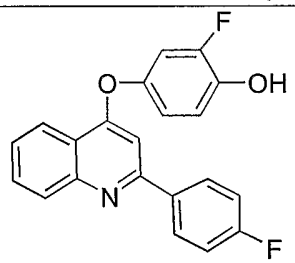
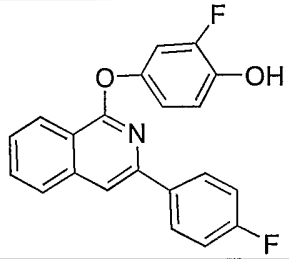
22.		Dimethyl-(3-phenyl-isoquinolin-1-yl)-amine
23.		Dimethyl-(2-phenyl-quinazolin-4-yl)-amine
24.		Dimethyl-(2-phenyl-quinolin-4-yl)-amine
25.		1-(2-Phenyl-quinolin-4-yl)-piperidin-4-ol
26.		1-(2-Phenyl-quinazolin-4-yl)-piperidin-4-ol
27.		1-(3-Phenyl-isoquinolin-1-yl)-piperidin-4-ol

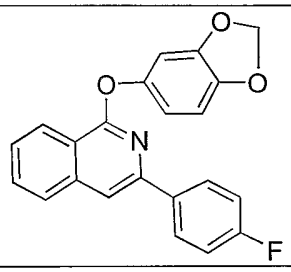
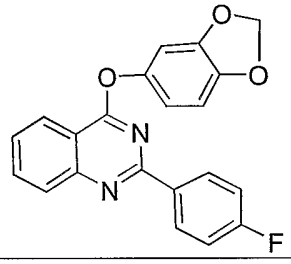
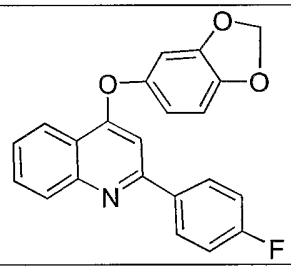
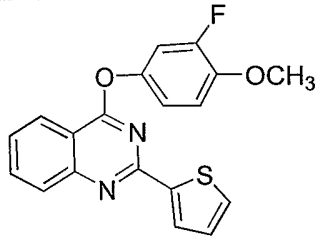
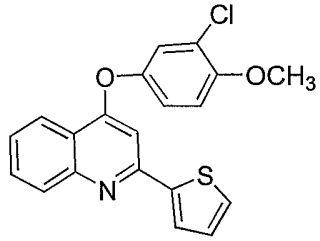
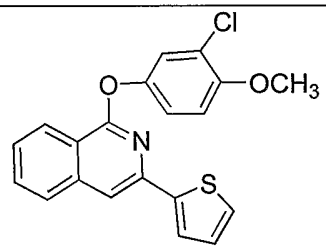
28.		4-[3-(3,4-Dimethoxy-phenyl)-isoquinolin-1-yl]-2-methyl-phenol
29.		4-[2-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methyl-phenol
30.		4-[2-(3,4-Dimethoxy-phenyl)-quinolin-4-yl]-2-methyl-phenol
31.		(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine
32.		(3-Fluoro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine

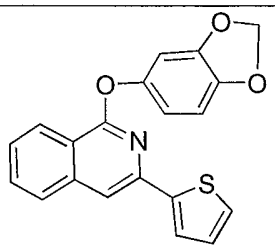
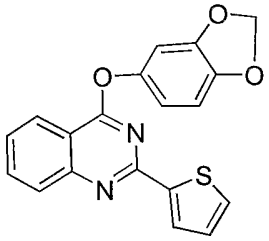
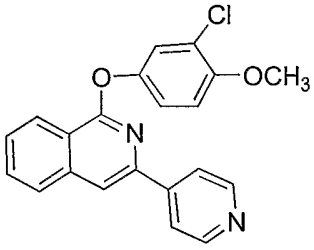
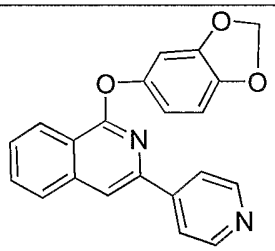
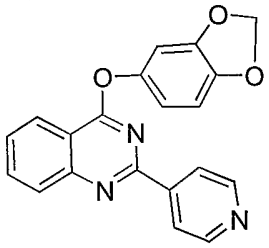
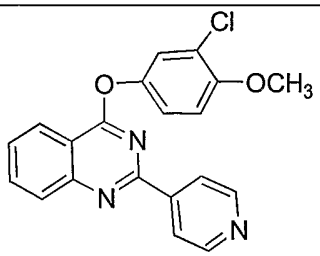
33.		4-(3-Chloro-4-methoxy-phenyl)-2-pyr idin-4-yl-quinazoline
34.		4-(3-Chloro-4-methoxy-phenyl)-2-pyr idin-4-yl-quinoline
35.		1-(3-Chloro-4-methoxy-phenyl)-3-pyr idin-4-yl-isoquinoline
36.		4-(4-Methylsulfanyl-phenyl)-2-pyrid in-4-yl-quinazoline
37.		4-(4-Methylsulfanyl-phenyl)-2-pyrid in-4-yl-quinoline
38.		1-(4-Methylsulfanyl-phenyl)-3-pyrid in-4-yl-isoquinoline

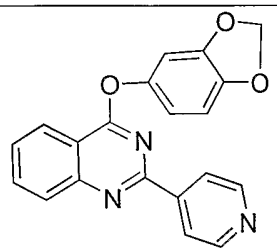
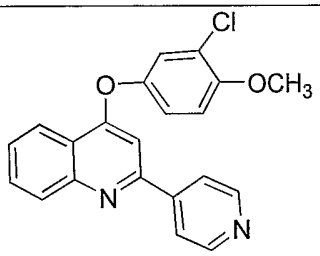
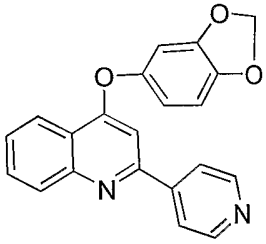
39.		4-(4-Methylsulfanyl-phenyl)-2-thiophen-2-yl-quinazoline
40.		4-(4-Methylsulfanyl-phenyl)-2-thiophen-2-yl-quinoline
41.		1-(4-Methylsulfanyl-phenyl)-3-thiophen-2-yl-isoquinoline
42.		1-(4-Methanesulfonyl-phenyl)-3-pyridin-4-yl-isoquinoline
43.		4-(4-Methanesulfonyl-phenyl)-2-pyridin-4-yl-quinazoline
44.		4-(4-Methanesulfonyl-phenyl)-2-pyridin-4-yl-quinoline

45.		4-Indol-1-yl-2-phenyl-quinazoline
46.		4-(5-Chloro-indol-1-yl)-2-phenyl-quinazoline
47.		1-Indol-1-yl-3-phenyl-isoquinoline
48.		1-(5-Chloro-indol-1-yl)-3-phenyl-isoquinoline
49.		4-(3-Fluoro-4-methoxy-phenoxy)-2-(4-fluoro-phenyl)-quinazoline
50.		1-(3-Fluoro-4-methoxy-phenoxy)-3-(4-fluoro-phenyl)-isoquinoline

51.		4-(3,4-Dimethoxy-phenoxy)-2-(4-fluoro-phenyl)-quinazoline
52.		4-(3,4-Dimethoxy-phenoxy)-2-(4-fluoro-phenyl)-quinoline
53.		1-(3,4-Dimethoxy-phenoxy)-3-(4-fluoro-phenyl)-isoquinoline
54.		2-Chloro-4-[3-(4-fluoro-phenyl)-isoquinolin-1-yloxy]-phenol
55.		2-Fluoro-4-[2-(4-fluoro-phenyl)-quinolin-4-yloxy]-phenol
56.		2-Fluoro-4-[3-(4-fluoro-phenyl)-isoquinolin-1-yloxy]-phenol

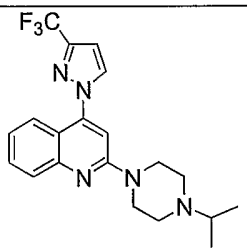
57.		1-(Benzo[1,3]dioxol-5-yloxy)-3-(4-fluoro-phenyl)-isoquinoline
58.		4-(Benzo[1,3]dioxol-5-yloxy)-2-(4-fluoro-phenyl)-quinazoline
59.		4-(Benzo[1,3]dioxol-5-yloxy)-2-(4-fluoro-phenyl)-quinoline
60.		4-(3-Fluoro-4-methoxy-phenoxy)-2-thiophen-2-yl-quinazoline
61.		4-(3-Chloro-4-methoxy-phenoxy)-2-thiophen-2-yl-quinoline
62.		1-(3-Chloro-4-methoxy-phenoxy)-3-thiophen-2-yl-isoquinoline

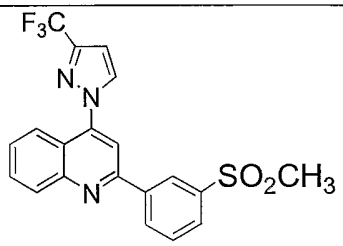
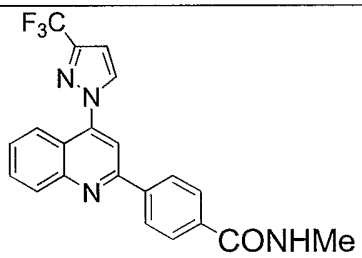
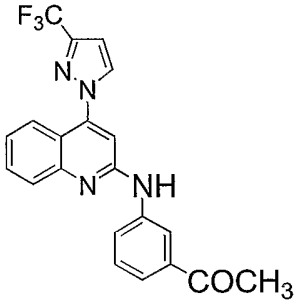
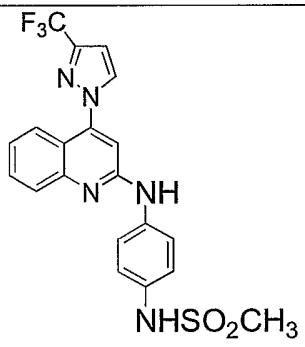
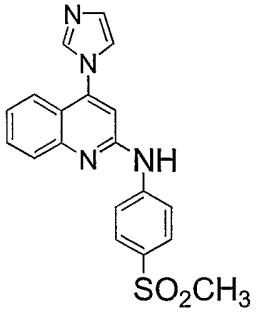
63.		1-(Benzo[1,3]dioxol-5-yloxy)-3-thiophen-2-yl-isoquinoline
64.		4-(Benzo[1,3]dioxol-5-yloxy)-2-thiophen-2-yl-quinazoline
65.		1-(3-Chloro-4-methoxy-phenoxy)-3-pyridin-4-yl-isoquinoline
66.		1-(Benzo[1,3]dioxol-5-yloxy)-3-pyridin-4-yl-isoquinoline
67.		4-(Benzo[1,3]dioxol-5-yloxy)-2-pyridin-4-yl-quinazoline
68.		4-(3-Chloro-4-methoxy-phenoxy)-2-pyridin-4-yl-quinazoline

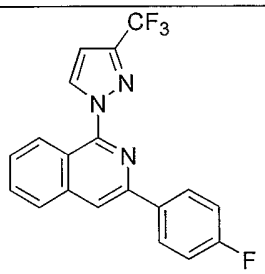
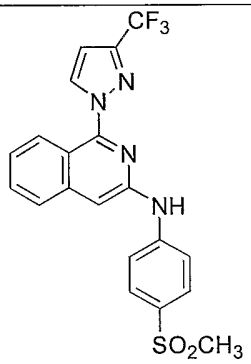
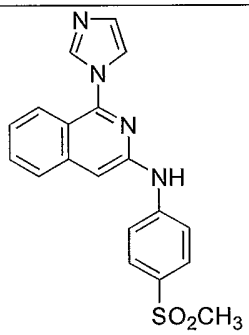
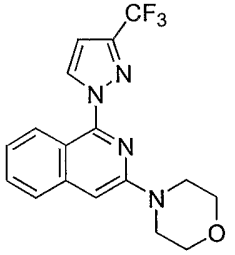
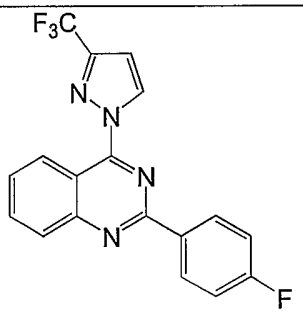
69.		4-(Benzo[1,3]dioxol-5-yloxy)-2-pyridin-4-yl-quinazoline
70.		4-(3-Chloro-4-methoxy-phenoxy)-2-pyridin-4-yl-quinoline
71.		4-(Benzo[1,3]dioxol-5-yloxy)-2-pyridin-4-yl-quinoline

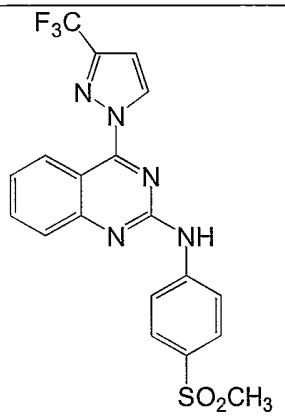
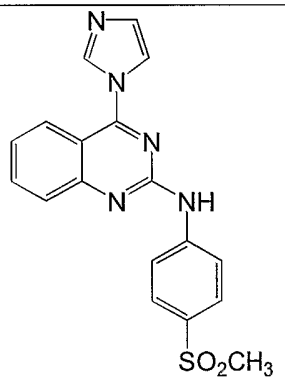
Additional representative compounds that constitute constructive examples of compounds in accordance with the present invention are presented below. Again, this table is not intended to be exclusive of the compounds of the present invention, but rather exemplary of the compounds that are encompassed by this invention.

Table 4. Representative constructive examples of compounds in accordance with the present invention.

Entry	Structure	Compound name
1.		2-(4-Isopropyl-piperazin-1-yl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline

2.		2-(3-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
3.		*N*-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-benzamide
4.		1-{3-[4-(3-Trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-phenyl}-ethanone
5.		*N*-{4-[4-(3-Trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-phenyl}-methanesulfonamide
6.		(4-Imidazol-1-yl-quinolin-2-yl)-(4-methanesulfonyl-phenyl)-amine

7.		3-(4-Fluoro-phenyl)-1-(3-trifluoromethyl-pyrazol-1-yl)-isoquinoline
8.		(4-Methanesulfonyl-phenyl)-[1-(3-trifluoromethyl-pyrazol-1-yl)-isoquinolin-3-yl]-amine
9.		(1-Imidazol-1-yl-isoquinolin-3-yl)-(4-methanesulfonyl-phenyl)-amine
10.		3-Morpholin-4-yl-1-(3-trifluoromethyl-pyrazol-1-yl)-isoquinoline
11.		2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinazoline

12.		(4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinazolin-2-yl]-amine
13.		(4-Imidazol-1-yl-quinazolin-2-yl)-(4-methanesulfonyl-phenyl)-amine

In this aspect of the present invention, compounds provided herein can be chiral or achiral, or they may exist as racemic mixtures, diastereomers, pure enantiomers, a prodrug, a tautomer or any mixture thereof. For chiral compounds, separate enantiomers, separate diastereomers, and any mixture of enantiomers, diastereomers, or both are encompassed herein. Further, the present invention also encompasses any combination of compounds provided herein, including any salts, including pharmaceutically acceptable and non-pharmaceutically acceptable salts, or any mixture thereof.

As used herein, the terms "pharmaceutically acceptable" salt or "pharmacologically acceptable" salt refers generally to a salt or complex of the compound or compounds in which the compound can be either anionic or cationic, and have associated with it a counter cation or anion, respectively, that is generally considered suitable for human or animal consumption. For example, a pharmaceutically acceptable salt can refer to a salt of a compound disclosed herein that forms upon reaction or complexation with an acid whose anion is generally

considered suitable for human or animal consumption. In this aspect, pharmacologically acceptable salts include salts with organic acids or inorganic acids. Examples of pharmacologically acceptable salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, propionate, lactate, maleate, malate, succinate, tartarate, and the like.

Salts may also be formed by deprotonating an acid moiety of the compound, such as a carboxylic acid moiety, OH, or NH, and the like, using a base such as an organic base, an inorganic base, an organometallic base, a Lewis base, a Brønsted base, or any combination thereof. In cases where compounds carry an acidic moiety, suitable pharmaceutically acceptable salts can include alkali metal salts, alkaline earth metal salts, or salts with organic basis, and the like. In this aspect, examples of alkali metal salts include, but are not limited to, sodium and potassium salts, and examples of salts with organic basis include, but are not limited to, meglumine salts, and the like. The pharmacologically acceptable salts can be prepared by conventional means. Additional examples of pharmaceutically acceptable salts, and methods of preparing such salts, are found, for example, in Berg et.al., J. Pharma. Sci, 66, 1-19 (1977).

In a further aspect, this invention also provides a composition comprising at least one compound as disclosed herein, including a composition comprising a pharmaceutically acceptable carrier and at least one compound as disclosed herein. In this aspect, the at least one compound can be present as a neutral compound, as a salt, or as any combination thereof. This invention also encompasses a composition comprising at least one compound as disclosed herein, and optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof.

Further, this invention encompasses a pharmaceutical composition, comprising at least one compound as disclosed herein, and optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof, wherein the pharmaceutical composition is in the form of a tablet, a capsule, a syrup, a cachet, a powder, a granule, a solution, a suspension, an emulsion, a bolus, a lozenge, a

suppository, a cream, a gel, a paste, a foam, a spray, an aerosol, a microcapsule, a liposome, or a transdermal patch.

In another aspect, this invention encompasses a pharmaceutical composition, comprising at least one compound as disclosed herein, and optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof; and further comprising an agent selected from a chemotherapeutic agent, an immunosuppressive agent, a cytokine, a cytotoxic agent, an anti-inflammatory agent, an antidyspilidemic agent, an antirheumatic agent, a cardiovascular agent, or any combination thereof.

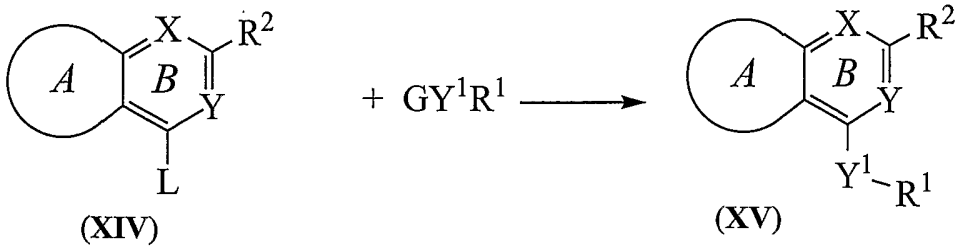
Another aspect of this invention is directed to using the compounds and compositions disclosed herein in a method of treating a condition or disease state mediated by the low expression of Perlecan, comprising administering an amount of at least one compound as disclosed herein, effective to induce Perlecan expression.

A further aspect of this invention is directed to using the compounds and compositions disclosed herein in a method of treating atherosclerosis, arthritis, restenosis, diabetic nephropathy, or dyslipidemia, comprising administering an effective amount of at least one compound as disclosed herein.

SYNTHETIC METHODS

The present invention, in another aspect, also provides a general process for the preparation of the bicyclo heterocyclic compounds disclosed herein. In one aspect, simple derivatization of a heterocycle, as illustrated by the reaction scheme given below, provides a synthetic entry to many of the substituted compounds of this invention.

Scheme 1



(XIV) **(XV)**

In this scheme, the bicyclic, heterocyclic precursor compound (**XIV**) comprises a leaving group, L. In one aspect, for example, L can be a halogen, an aryloxy, an alkylsulfinyl, an alkylsulfonyl such as trifluoromethanesulfonyloxy, an arylsulfinyl, an arylsulfonyl, a silyloxy, a cyano, a pyrazolo, a triazolo, and the like, or similar leaving groups. Other substituents on heterocyclic precursor compound (**XIV**) and heterocyclic product (**XV**) are as defined herein for structure (**I**). Thus, compound (**XIV**) can be converted to heterocyclic product (**XV**) by its reaction with a compound of formula GY^1R^1, wherein G can be selected from, for example, hydrogen, NH_2, NHR^5 wherein R^5 is defined as it is for structure (**I**), OH, SH, $B(OH)_2$, Li, MgZ wherein Z is typically a halogen, and the like. In one aspect, when G is NHR^5, R^1 and R^5 together can form an optionally substituted cyclic ring along with an adjacent N atom, which can optionally comprise one or more hetero atoms selected from oxygen, nitrogen or sulfur.

In another aspect, the reaction presented in the scheme above can be performed in presence of a base such as sodium hydroxide, potassium hydroxide, potassium carbonate, and the like. Similarly, the reaction presented in the scheme above also can be performed in the presence of a Lewis acid such as aluminum chloride ($AlCl_3$), or a transition metal catalyst such as a palladium catalyst. For example, a suitable palladium catalyst can be selected from tetrakis(triphenylphosphine)palladium(0) [$(PPh_3)_4Pd$], bis(triphenylphosphine)-palladium(II)chloride [$(PPh_3)_2PdCl_2$], and the like, including a combination thereof. In one aspect, the reaction shown in the scheme above can be carried out in a solvent such as acetone, dimethylformamide (DMF), dimethylacetamide (DMA), benzene, toluene, and the like. In another aspect, for example, the temperature of the reaction can be from about 25°C to about 150°C, though temperatures lower and higher are possible, and the duration of the reaction can be, for example, from about 2 hours to about 24 hours or more.

The following references relate generally to the quinoline, isoquinoline, and quinazoline classes of compounds: Preparation of quinolines and quinazolines as TGF-beta inhibitors (WO 2004081009); Preparation of quinoline-2,4-diamines as N-

type calcium channel antagonists for the treatment of pain (WO 2003018561); Preparation of substituted quinazolines and related derivatives as inhibitors of IL-12 (WO 2005046698); Preparation of quinoline potassium channel inhibitors (WO 2005030129); Preparation of 4-anilino substituted quinazolines as inhibitors of epidermal growth factor receptor kinases (WO 2004013091); Methods for improvement of lung function using TGF-β inhibitors (WO 2004010929); Treatment of fibroproliferative disorders using TGF-β inhibitors (WO 2003097615); Preparation of quinazolines as TGF-β and/or p38-α kinase inhibitors (U.S. Patent No. 6,476,031); Antagonism of immunostimulatory CpG-oligonucleotides by 4-aminoquinolines and other weak bases (WO 2000076982); 4-Aminoquinazoline derivatives, and their use as medicine (EP 579496); Preparation of quinoline derivatives as immunostimulants (WO 9303030); Preparation of (heterocyclylvinyl)mevalonic lactone analogs as antiatherosclerotics (EP 535548); Preparation of diaminoquinazoline derivatives as ulcer inhibitors (U.S. Patent No. 5,064,833); Preparation, testing, and formulation of 2,4-diaminoquinazolines as ulcer inhibitors (WO 8905297); Quinolinylheptenoic acid derivatives as anticholesteremics, their preparation, and formulations containing them (EP 304063); Preparation of quinazolines as modulators of ion channels (WO 2004078733). Applicants reserve the right to proviso out or to restrict from any claim currently presented, or from any claim that can be presented in this or any further application based upon this disclosure, including claims drawn any genus or subgenus disclosed herein, any compound or group of compounds disclosed in any reference, including any reference provided herein.

The following general reaction schemes detail the synthetic approaches to the bicyclic heterocyclic compounds disclosed herein.

Compounds disclosed herein could be prepared as shown in Schemes 1-5 and as illustrated in the Examples by using standard synthetic methods and the starting materials, which are either commercially available or can be synthesized from commercially available precursors using synthetic methods known in the art, or variations thereof as appreciated by those skilled in the art. Each variable in the following schemes refer to any group consistent with the description of the compounds provided herein.

The following general procedures could be used in the reactions schemes and in the Examples provided herein.

Halogenation could be carried out by using reagents such as phosphorus oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), and the like, for example, at a temperature from about 80°C to about 120°C, for about 4 to about 8 hours, followed by pH adjustment of resultant mixture to a pH from about 6 to about 7.

Amination could be carried out by using amines in presence of a solvent chosen from acetone, acetonitrile, dimethylformamide, dimethylacetamide and the like, with or with out a base. Suitable bases include triethylamine, N,N-diisopropyl ethyl amine, potassium carbonate, sodium carbonate, sodium hydride, and the like. The reaction temperature was typically from about 20°C to about 120°C. The duration of the reaction was typically in the range of from about 4 hours to about 20 hours.

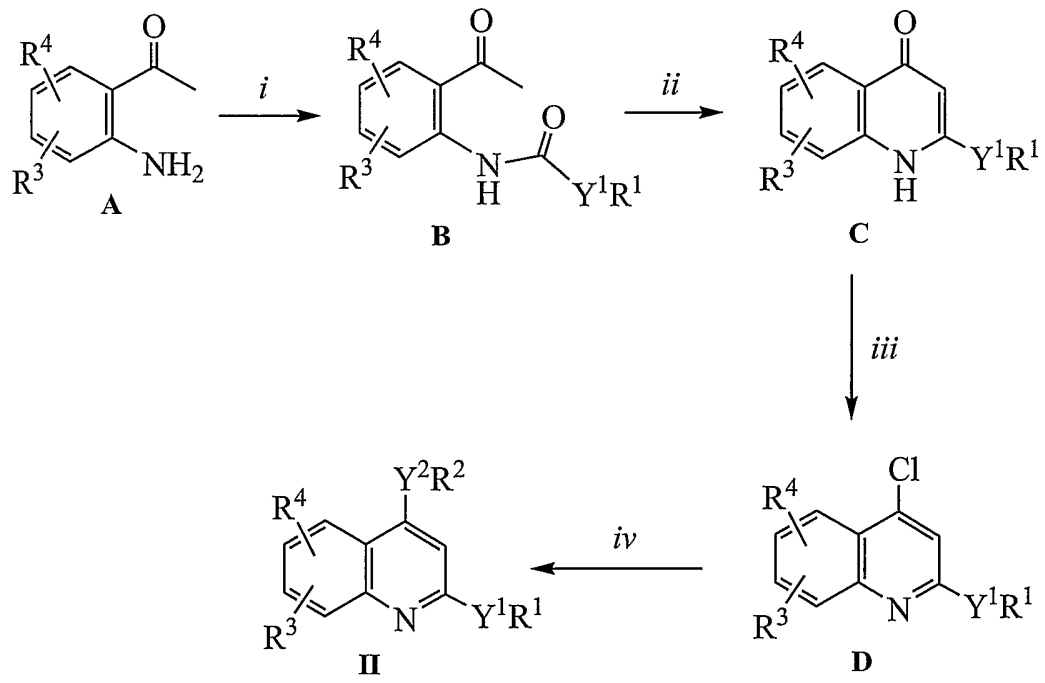
Arylation was carried out by aryl boronic acids, for example in the presence of a palladium catalyst and a base such as sodium carbonate, potassium carbonate, sodium or potassium *tert*- butoxide, potassium phosphate and the like, at ambient temperature or elevated temperatures using various inert solvents. Examples of suitable solvents include, but are not limited to toluene, dioxane, DMF, n-methyl pyrolidine, ethylene glycol, dimethyl ether, diglyne, and acetonitrile. Commonly employed palladium catalysts include [tetrakis-(triphenylphosphine) palladium (0)] [$(PPh_3)_4Pd$], tris(dibenzeledine acetone)dipalladium (0) or palladium (II) acetate[$Pd(OAc)_2$], [bis(triphenylphosphine)palladium(II)chloride] [$(PPh_3)_2PdCl_2$] (Suzuki reaction, Miyaura and Suzuki (Chemical Reviews **1995**, *95*, 2457).

Thus one further aspect of the invention relates to the processes of preparing compounds of formulas provided herein. Any compound of any formula disclosed herein can be obtained using procedures provided in the reaction Schemes, as well as procedures provided in the Examples, by selecting suitable starting materials and following analogous procedures. Thus, any compound of any formula disclosed or exemplified herein, can be obtained by using the appropriate starting materials and appropriate reagents, with the desired substitutions, and following procedures analogous to those described herein.

Therefore, it will be readily understood by one of ordinary skill, that the reaction schemes disclosed herein can be adapted to prepare any compound of this disclosure, therefore any discussion of a particular step in a reaction scheme is intended to reflect one method or one set of conditions that can be used to carry out that step. This discussion of a particular step is not intended to be limiting, but rather exemplary, of one particular method and set of conditions by which that step can be effected. For example, when a reaction scheme illustrates a synthetic method to prepare a compound of formula (**IIa**), it is intended that the substituents R^1, R^2, R^3, R^4, and Y^1 illustrated on the bicyclic heterocyclic core include at least those substituents identified in the description of compound (**II**) herein, but also include other substituents that could be employed in any step in the reaction scheme or in any precursor, to prepare any compound of any formula disclosed or exemplified herein.

In one aspect of this invention, compounds of this invention can be prepared as follows, as illustrated for compounds of formula (**II**).

Scheme 2



The Scheme 2 starting materials are various 2-amino acetophenones of formula **A**. Compounds of formula **A** are either commercially available with the appropriate substitutions, or are well known in the chemical literature and can be readily prepared. Representative steps of Scheme 2 include the following.

Step i: The 2-amino acetophenones of formula **A** can be converted to an amide of formula **B** either directly or by way of an acid chloride. This conversion can be achieved by treating the acid chloride in the presence of a base such as triethylamine (TEA) in a suitable solvent such as dichloromethane (DCM). Typically, this reaction can be performed at from between about 0°C and about 40°C.

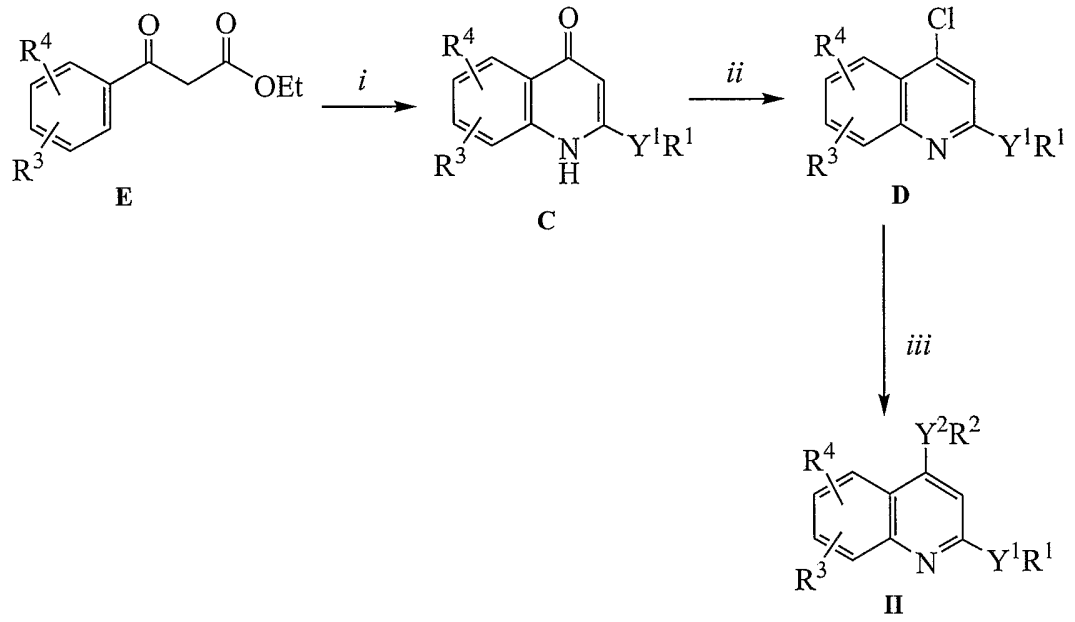
Step ii: The compound of formula **B** can be treated with a base such as metal alkoxides, for example potassium *t*-butoxide, in a polar solvent such as *t*-butanol, typically at a temperature from about 20°C to about 100°C.

Step iii: The compound of formula **C** can be treated with a large excess of suitable chlorinating reagent such as $POCl_3$ or phenyl phosphonyl dichloride in the presence of a tertiary amine such as TEA, at elevated temperatures, for a period of from about 8 to about 48 hours, to provide the corresponding chloro compound of formula **D**.

Step iv: A solution of the chloride of formula **D** and an amine such as R^1Y^1H in a suitable solvent such as isopropanol can be stirred at elevated temperatures for a time period from about 1 hour to about 24 hours, to provide the corresponding compounds of formula **II**.

In another aspect of the present invention, compounds of this invention can be prepared as follows, as illustrated for compounds of formula (**II**).

Scheme 3



Compounds of formula **E** are either commercially available with the appropriate substitutions, or are well known in the chemical literature and can be readily prepared. Representative steps of Scheme 3 include the following.

Step i: Ethyl benzoylacetates of formula **E** can be converted to compounds of formula **C** upon their reaction with HY^1R^1 in presence of a reagent such as polyphosphoric acid.

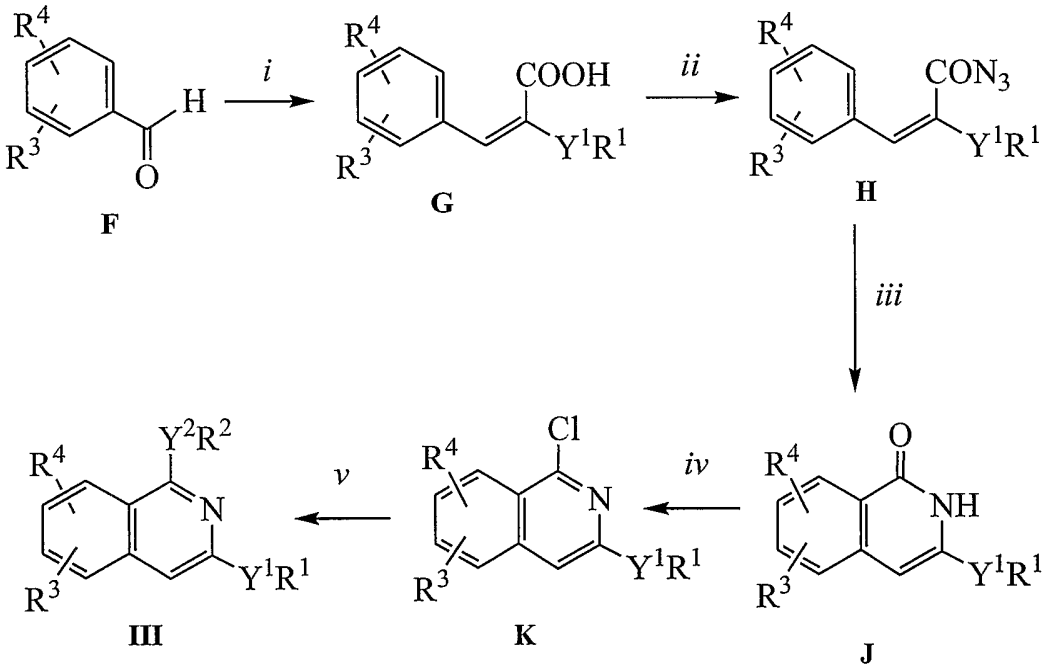
Step ii: Compounds of formula **C** can be treated with a large excess of a suitable chlorinating reagent such as, for example, $POCl_3$ or phenyl phosphonyl dichloride, in the presence of, for example, a *tertiary* amine such as triethyl amine (TEA). In one aspect, typically these reactions can be performed at elevated temperatures for time periods ranging from about 8 hours to about 48 hours, to afford the corresponding chloro compound of formula **D**.

Step iii: A solution of the chloride of formula **D** and a compound of formula R^2Y^2H, including a phenyl or substituted phenyl compound of the formula R^2Y^2H (wherein Y^2 represents a direct bond between about R^2 and H) can be reacted in a suitable solvent such as 1,2-dichloroethane, in presence of

$AlCl_3$. In one aspect, these reactions can be conducted at elevated temperatures for a time period from about 1 to about 24 hours, to provide the corresponding compounds of formula **II**.

In still another aspect of this invention, compounds of this invention can be prepared as follows, as illustrated for compounds of formula (**III**).

Scheme 4



Desired compounds of formula **F** are either commercially available with the appropriate substitutions, or are well known in the chemical literature and can be readily prepared. Representative steps of Scheme 4 include the following.

Step i: Acetophenone compounds of formula **F** can be converted to compounds of formula **G** upon the reaction of **F** with, for example, $R^1Y^1CH_2COOH$ in presence of acetic anhydride, and an organic base such as NEt_3.

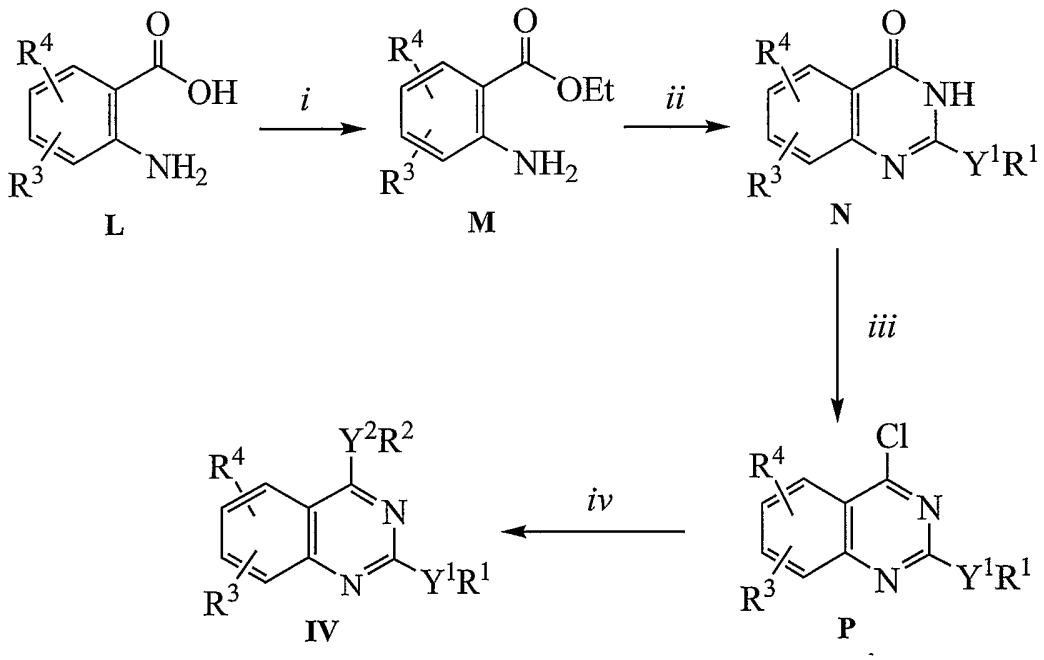
Step ii: Compounds of formula **G** can be converted to azides of formula **H** upon reaction **G** with, for example, NaN_3, in the presence of a reagent such as ethyl chloroformate and base such as NEt_3.

Step iii: Azide compounds of formula **H** can be converted to isoquinolone compounds of formula **J** in presence of a base such as tributylamine and solvent such as diphenylether, typically at an elevated temperature.

Steps iv and v: Compounds of formula **III** can be obtained by Steps iv and v, for example, which are conducted by the methods described in Scheme 2, Steps iii and iv, respectively.

Yet another aspect of this invention provides for compounds of this invention that can be prepared as follows, as illustrated for compounds of formula (**IV**).

Scheme 5



Compounds of formula **L** are either commercially available with the appropriate substitutions, or are well known in the chemical literature and can be readily prepared. Representative steps of Scheme 5 include the following.

Step i: Vacious anthranilic acids of formula **L** can be converted to esters of formula **M** by, for example, the reaction of **M** with alcohols in presence of $SOCl_2$.

Step ii: The esters of formula **M** can be converted to quinazolones of formula **H** by, for example, reacting **M** with compounds having the formula $R^1Y^1C{\equiv}N$. For example, $R^1Y^1C{\equiv}N$ can be cyano aromatic compounds, such as 4-cyanopyridine or cyanobenzene.

Steps iii and iv: Compounds of formula **IV** can be obtained, for example, by Steps iii and iv, which can be conducted by the methods described in Scheme 2, Steps iii and iv, respectively.

PRODRUGS

In another aspect of this invention, alternatively, the compounds can be formulated and administered in a prodrug form. In general, prodrugs comprise functional derivatives of the claimed compounds which are capable of being enzymatically activated or converted into the more active parent form. Thus, in the treatment methods of the present invention, the term "administering" encompasses the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Wihnan, 14 Biochem. Soc. Trans. 375-82 (1986); Stella et al., Prodrugs: A Chemical Approach to Targeted Drug Delivery in Directed Drug Delivery 247-67 (1985).

The prodrugs of present invention include, but are not limited to derivatives of carboxylic acid, sulfonamide, amine, hydroxyl, and the like, including other functional groups and including any combination thereof.

In another aspect, this invention provides a pharmaceutical composition, comprising one or more compounds of any formula in any combination described above and optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof. In a related aspect, this invention affords a method of treating a condition or disease state mediated by the low expression of Perlecan, comprising administering at least one compound as disclosed herein, in an amount effective to

induce Perlecan expression. In a related aspect, this invention also provides a method of treating atherosclerosis, arthritis, restenosis, diabetic nephropathy, or dyslipidemia, comprising administering an effective amount of at least one compound as disclosed herein.

CELLULAR PROLIFERATION

Without being held to a particular theory, it is believed that many vascular conditions or diseases, such as cardiovascular diseases, organ transplant sequellae, vascular occlusive conditions including, but not limited to, neointimal hyperplasia, restenosis, transplant vasculopathy, cardiac allograft vasculopathy, atherosclerosis, and arteriosclerosis, are caused by or have collateral damage due to unwanted cellular proliferation, such as SMC hyperplasia.

In one aspect, a compound of the present invention or a composition comprising the compound attenuates or inhibits proliferation of a cell. In one aspect, the cell is a SMC. In other aspects, the present invention provides a method for treating a condition or disease associated with proliferation of a cell in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof. In one aspect, the condition or disease is a neoplasia. In another aspect, the condition or disease is SMC hyperplasia. In other aspects, the condition or disease is a cardiovascular disease, an organ transplant sequellae, or a vascular occlusive condition. In one aspect, the vascular occlusive condition comprises neointimal hyperplasia, restenosis, transplant vasculopathy, cardiac allograft vasculopathy, atherosclerosis, or arteriosclerosis.

Compounds that are effective in inhibiting SMC proliferation can be administered to a mammalian subject suspected of having or who has, for example, vasculopathy or who has undergone angioplasty or other procedures damaging to the endothelium.

Effective amounts are administered to the subject in dosages and formulations that are safe and effective, including, but not limited to, the ranges taught herein.

As disclosed herein, compositions comprising at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof, can be used in conjunction with other therapeutic agents or in methods optionally comprising steps such as altered patient activities, including, but not limited to, changes in exercise or diet.

Examples of compounds of the present invention that can at least affect cellular proliferation are shown in the following table, as measured by the assays taught herein.

Table 5. Examples of compounds that at least affect cellular proliferation.

Entry	Compound
1.	(3-Chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine
2.	(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine
3.	4-(2-Pyridin-4-yl-quinazolin-4-yl)-benzene-1,3-diol
4.	4-(2-Phenyl-quinazolin-4-yl)-benzene-1,3-diol
5.	(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine
6.	(3-Chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine
7.	(3-Chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
8.	(3-Fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine
9.	(4-Chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
10.	4-Indol-1-yl-2-phenyl-quinoline
11.	2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
12.	2-(4-Fluoro-phenyl)-4-imidazol-1-yl-quinoline
13.	2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
14.	2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
15.	2-(4-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline

16.	2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
17.	(4-Trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine
18.	2-Morpholin-4-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
19.	N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide
20.	N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide

Proteoglycan (PG) expression can affect cellular proliferation. For example, increased expression of a PG such as, for example, a heparin sulfate proteoglycan (HSPG) can attenuate or inhibit cellular proliferation. A compound as described herein or a composition comprising the compound is for example useful as an antiproliferative agent.

As used herein, the term "proteoglycan" also can refer to an active fragment of a proteoglycan.

As used herein, the term "expression" refers to production and/or activity of a substance such as, for example, a protein or a second messenger. In the case of a substance comprising a protein, production can include, for example, transcription of the DNA sequence, translation of the corresponding mRNA sequence, posttranslational modification (e.g., glycosylation, disulfide bond formation, etc.), nuclear transport, secretion/exocytosis, and/or assembly. Non-limiting examples of "activity" of a substance include binding of the substance to a ligand or to a receptor, catalytic activity, signaling activity, the ability to stimulate gene expression, antigenic activity, activity in modulating or maintaining cell/cell interactions (e.g., adhesion), and/or activity in maintaining a structure of a cell (e.g., cell membranes, cytoskeleton). One skilled in the art knows that activity modulation can arise via a variety of mechanisms such as, for example, phosporylation and/or dephosphorylation.

As used herein, the term "affect" refers to direct and/or indirect affects. For example, a compound affecting "expression" of a HSPG via an increase in the rate of

transcription of the corresponding gene may itself directly interact with the transcriptional machinery and/or may modulate other proteins or factors that cause an increase in the rate of transcription (*e.g.*, activating a transcription factor).

In one aspect, a compound of the present invention or a composition comprising the compound increases expression of a HSPG. Non-limiting examples of a HSPG include a syndecan, a glypican, and a perlecan. Perlecan is a major extracellular HSPG and can be found, for example, in the blood vessel matrix. Perlecan can interact with extracellular matrix proteins, growth factors, and receptors. Besides blood vessels, perlecan also is present in other basement membranes and extracellular matrix structures.

In one aspect, the present invention provides a method for treating a condition or disease mediated by low expression of a perlecan in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof, wherein the effective amount is sufficient to increase perlecan expression. In another aspect, the present invention provides a method for treating a condition or disease in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof, wherein the condition or disease is atherosclerosis, arthritis, restenosis, diabetic nephropathy, or dyslipidemia.

Examples of a condition or disease mediated by low expression of a HSPG such as, for example, perlecan are shown in the following table.

Table 6. Conditions or disease states mediated by the low expression of perlecan in a human or an animal.

Condition or Disease State	Reference
Atherosclerosis, cardiovascular	1. Endogenous heparin activity deficiency: the 'missing link' in atherogenesis? Atherosclerosis. 2001 Dec;159(2):253-60. 2. Holliman J et al, Relationship of sulfated glycosaminoglycans and cholesterol content in normal and atherosclerotic human aorta 3. Duan W, Paka L, Pillarisetti S. Distinct effects of glucose and glucosamine on vascular endothelial and smooth muscle cells:

	evidence for a protective role for glucosamine in atherosclerosis. Cardiovasc Diabetol. 2005 Oct 5;4:16. 4. Pillarisetti, S. Lipoprotein modulation of subendothelial heparan sulfate proteoglycans (perlecan) and atherogenicity. Trends Cardiovasc Med. 2000 Feb;10(2):60-5.
Restenosis	5. Paka L, Goldberg IJ, Obunike JC, Choi SY, Saxena U, Goldberg ID, Pillarisetti S. Perlecan mediates the antiproliferative effect of apolipoprotein E on smooth muscle cells. An underlying mechanism for the modulation of smooth muscle cell growth? J Biol Chem. 1999 Dec 17;274(51):36403-8. 6. Nugent MA, Nugent HM, Iozzo RV, Sanchack K, Edelman ER. Perlecan is required to inhibit thrombosis after deep vascular injury and contributes to endothelial cell-mediated inhibition of intimal hyperplasia. Proc Natl Acad Sci U S A. 2000 Jun 6;97(12):6722-7.
Thrombosis	7. Nugent MA, Nugent HM, Iozzo RV, Sanchack K, Edelman ER. Perlecan is required to inhibit thrombosis after deep vascular injury and contributes to endothelial cell-mediated inhibition of intimal hyperplasia. Proc Natl Acad Sci U S A. 2000 Jun 6;97(12):6722-7.
Diabetic kidney disease	8. Menne J, Park JK, Boehne M, Elger M, Lindschau C, Kirsch T, Meier M, Gueler F, Fiebeler A, Bahlmann FH, Leitges M, Haller H. Diminished loss of proteoglycans and lack of albuminuria in protein kinase C-alpha-deficient diabetic mice. Diabetes. 2004 Aug;53(8):2101-9 9. Jensen T. Pathogenesis of diabetic vascular disease: evidence for the role of reduced heparan sulfate proteoglycan. Diabetes. 1997 Sep;46 Suppl 2:S98-100
Inflammation	10. Pillarisetti, S, Obunike JC, Goldberg IJ. Lysolecithin-induced alteration of subendothelial heparan sulfate proteoglycans increases monocyte binding to matrix. J Biol Chem. 1995 Dec 15;270(50):29760-5 11. Rops AL, van der Vlag J, Lensen JF, Wijnhoven TJ, van den Heuvel LP, van Kuppevelt TH, Berden JH. Heparan sulfate proteoglycans in glomerular inflammation. Kidney Int. 2004 Mar;65(3):768-85.

Screening methods for identifying and determining the effects of a compound that increases proteoglycan expression, such as HSPG expression, are disclosed in U.S. Patent Application Serial No. 10/091,357. Assays for determining the effects of the compound *in vivo* are also known to those skilled in the art. In general, the method comprises adding the compound to an assay and determining its affect on HSPG expression, including, but not limited to, syndecan expression, glypican expression and perlecan expression, for example, syndecans 1, 2 and 4; and glypican-1. In another aspect, perlecan expression is increased/induced or decreased/blocked in cells by certain inducers or inhibitors and the response is measured. Compounds of

the present invention are then added to a replicate assay and the effect on perlecan induction is determined. Using such methods, compounds are determined that can either increase or decrease perlecan expression, or that have no effect at all. Those compounds that are effective as therapeutic agents can then be used in animals, humans or patients having a condition or disease associated with cellular proliferation as described herein.

In yet another aspect, a method for determining a compound that affects cellular proliferation comprises adding the compound or a composition comprising the compound suspected of affecting SMC proliferation to SMCs in growth medium or serum-free medium. The change in cell proliferation can be measured by methods known to those skilled in the art, such as incorporation of labeled nucleotides into dividing cells' DNA, and compared to the proliferation of cells which are not treated with the compound. Other measurements include directly determining levels of HSPG expression by measuring the amount or change in amount of HSPG such as with ELISA for HSPGs, and compared to the amount of HSPG synthesis in untreated cells. Other indirect or direct measurements are contemplated by the present invention and are known to those skilled in the art. For example, such methods include, but are not limited to, measurement of RNA levels, RT-PCR, Northern blotting, Western blotting promoter-based assays to identify compounds that affect one or more proteoglycans and assays for proteoglycan biological activity shown by recombinant proteins, partially purified proteins, or lysates from cells expressing proteoglycans in the presence or absence of compounds of interest.

An assay for identifying and determining an effect of a compound of the present invention comprises identifying compounds that interact with the promoter or enhancer regions of a gene (i.e., gene regulatory regions), or interact and affect proteins or factors that interact with the promoter or enhancer region, and are important in the transcriptional regulation of the protein's expression. For example, if perlecan were the protein, in general, the method comprises a vector comprising regulatory sequences of the perlecan gene and an indicator region controlled by the regulatory sequences, such as an enzyme, in a promoter-reporter construct. The protein product of the indicator region is referred to herein as a reporter enzyme or

reporter protein. The regulatory region of the sequence of perlecan comprises a range of nucleotides from approximately -4000 to +2000 wherein the transcription initiation site is +1, more preferably, from -2500 to +1200, most preferably, from -1500 to +800 relative to the transcription initiation site. One skilled in the art knows that a gene may have one or more regulatory regions which may exist at a relatively near or relatively far distance from the transcription start site of the gene. One or more compounds according to the present invention can affect one or more known or unknown regulatory regions of a particular gene.

Cells are transfected with a vector comprising the promoter-reporter construct and then treated with one or more compositions comprising at least one compound of the present invention. For example, the transfected cells are treated with a composition comprising a compound suspected of affecting the transcription of perlecan and the level of activity of the perlecan regulatory sequences are compared to the level of activity in cells that were not treated with the compound. The levels of activity of the perlecan regulatory sequences are determined by measuring the amount of the reporter protein or determining the activity of the reporter enzyme controlled by the regulatory sequences. An increase in the amount of the reporter protein or the reporter enzyme activity shows a stimulatory effect on perlecan, by positively effecting the promoter, whereas a decrease in the amount or the reporter protein or the reporter enzyme activity shows a negative effect on the promoter and thus, on perlecan.

Additionally, the present invention comprises methods and compositions that can be used with gene therapy methods and composition, such as those gene therapy methods comprising administering compositions comprising nucleic acids that affect the synthesis or expression of HSPGs, particularly perlecan. Such methods and compositions are disclosed in U.S. Patent Application Serial No. 10/091,357.

GLYCOSIDASE MODULATION

The present invention also provides methods and compositions for modulating glycosidase expression such as, for example, heparanase expression.Without being held to a particular theory, it is believed thatglycosidases and their substrates, such as

proteoglycans or glycated proteins, are aspects of a variety of conditions or diseases such as, for example, vascular conditions, including those conditions discussed supra, proteoglycan-associated diseases, associated diseases with vascular components, including but not limited to, kidney disease, ischemic heart disease, cardiovascular disease, generalized vascular disease, proliferative retinopathy, macroangeopathy, inflammatory diseases and metastatic diseases such as cancer, cellular proliferative conditions, and solid and blood borne tumors or other oncological conditions. In some aspects, a compound according to the present invention is, for example, useful for treating vascular, inflammatory, metastatic, and systemic conditions or diseases by affecting one or more substrates of one or more glycosidases.

Examples of compounds of the present invention that at least affect glycosidase expression are shown in the following table, as measured by the assays taught herein.

Table 7. Examples of compounds that at least affect glycosidase expression.

Entry	Compound
1.	(3-Chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine
2.	(3-Chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine

In some aspects, the present invention provides a method for treating or preventing a condition or disease in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof. In other aspects, the method comprises administering to the subject a composition comprising a therapeutically-effective amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof, wherein the therapeutically-effective amount is sufficient to attenuate or inhibit expression of a glycosidase. In one aspect, the glycosidase is heparanase. In some aspects, the condition or disease comprises cancer including, but not limited to, malignant and non-malignant cell growth, and the like. In another aspect, the

condition or disease is an inflammatory condition or an autoimmune disease. In one aspect, the condition or disease is diabetic vasculopathy.

In one aspect, the present invention provides a method for treating or preventing an autoimmune condition or disease in a mammalian subject, the method comprising administering to the subject a composition comprising a therapeutically-effective amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof. In another aspect, the autoimmune condition or disease is rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disesease, thrombocytopenia, graft rejection of any organ or tissue, kidney translplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, type III hypersensitivity

reactions, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, anti-phospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, autoimmune hemolytic anemia, autoimmune hepatitis, idiopathic pulmonary fibrosis, scleroderma, diabetes mellitus, chronic active hepatitis, vitiligo, vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, ankylosing spondylitis, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, Graves' disease, Guillain-Barré, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura (ITP), IgA nephropathy, insulin dependent diabetes, juvenile arthritis, lichen planus, ménière's disease, multiple sclerosis, pemphigus vulgaris, polyarteritis nodosa, Cogan's syndrome, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, Sjögren's syndrome, stiff-man syndrome, Takayasu arteritis, temporal arteritis/giant cell arteritis, Wegener's granulomatosis; okt3 therapy, anti-cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited toasthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like.

Illustrative assays or methods suitable for identifying compounds that affect heparanase expression are disclosed in the references cited individually below and incorporated herein by reference.

U. S. Patent No. 4,859,581.

U.S. Patent Application Serial No. 09/952,648

Goshen et al., 2 MOL. HUM. REPROD. 679-84 (1996).

Nakajima et al., 31 CANCER LETT. 277-83 (1986).

Vlodasky et al., 12 INVASION METASTASIS 112-27 (1992).

Freeman and Parish, 325 BIOCHEM. J. 229-37 (1997).

Kahn and Newman, 196 ANAL. BIOCHEM. 373-76 (1991).

INFLAMMATION MODULATION

In various other aspects, the present invention provides a method for treating or preventing an inflammatory condition or disease. Without being held to a particular theory, pharmacological inhibition of AGE-induced cell activation provides the basis for therapeutic intervention in many diseases, notably in diabetic complications and Alzheimer's disease. Therapeutic approaches for inhibition of AGE-induced inflammation include, but are not limited to, blocking the glycation of proteins, blocking AGE interactions with receptors, and blocking AGE-induced signaling or signaling-associated inflammatory responses. Compounds described herein are for example useful for modulating inflammation including, but not limited to, inhibiting inflammation and/or its associated cell activation by glycated proteins or AGE, blocking the glycation of proteins, blocking AGE interactions with receptors, blocking AGE-induced signaling or signaling-associated inflammatory responses, affecting cytokine expression, AGE formation, AGE cross-linking, or affecting expression of other inflammation-related molecules including, but not limited to IL-6, VCAM-1, or AGE-induced MCP-1 (monocyte chemoattractant protein 1).

The term "inflammatory condition or disease" herein refers to any condition or disease directly or indirectly associated with inflammation including, for example, cell activation by glycated proteins or AGE. An inflammatory condition or disease can be acute or chronic. Illustratively, inflammatory conditions or diseases include, without

limitation, inflammation associated with accumulation or presence of glycated proteins or AGE, vascular complications of type I or type II diabetes, atherosclerosis, rheumatoid arthritis, osteoarthritis, intraoccular inflammation, psoriasis, and asthma.

Examples of compounds of the present invention that modulate inflammation are shown in the following table, as measured by the assays taught herein.

Table 8. Examples of compounds of the present invention that affect inflammation.

Entry	Compound
1.	(3-Chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine
2.	4-(2-Pyridin-4-yl-quinazolin-4-yl)-benzene-1,3-diol
3.	4-(2-Phenyl-quinazolin-4-yl)-benzene-1,3-diol
4.	(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine
5.	(3-Chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine
6.	(3-Chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
7.	(3-Fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine
8.	(4-Chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine
9.	2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
10.	2-(4-Fluoro-phenyl)-4-imidazol-1-yl-quinoline
11.	2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
12.	2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
13.	2-(4-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
14.	2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
15.	(4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine
16.	(4-Trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine

17.	2-Morpholin-4-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline
18.	N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide
19.	N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide

Inclusion of a compound in any table disclosed herein is not to be seen as limiting, in that the compound included in a specific table has at least the affect shown for inclusion in the table and may have additional other affects. Nor are the tables to be seen as limiting in that the compounds listed in a particular table are the only compounds disclosed herein that have that affect.

Assays for determining the ability of a compound of the present invention to modulate inflammation, or more specifically, attenuate or inhibit glycated protein- or AGE-induced inflammation are described herein and in U.S. Patent Application Serial No. 10/026,335 and 09/969,013, which are incorporated herein by reference.

In some assays, for example, the specific expression (i.e., production or activity) of a substance or biological component involved in a known cellular response is measured. The assays provide a measurable response in which the affect of a compound is determined.

One assay, for example, comprises measuring the effect of a compound on a known inflammatory response of cells to a stimulating agent such as, for example, a glycated protein.

In another assay, for example, cytokine expression of stimulated cells can be measured in control cells and cells exposed to a compound described herein. Illustratively, a stimulated cell can be an endothelial cell stimulated with glycated protein. Comparison of the cytokine profile of control cells (*i.e.*, baseline) versus cells exposed to the compound can indicate the affect of the compound on cytokine expression and, hence, inflammation. The cytokine profile can be qualitative and/or quantitative. For example, where the cytokine is a secreted protein, the amount of the cytokine present in the media can be quantitated using antibodies specific to the cytokine. The compound may have an inhibitory effect, stimulatory effect, or no

effect at all. Besides cytokines, expression of other factors or parameters can be determined using such assays.

One or more compounds can be added to a screening assay. Combinations or mixtures of compounds can be added. Different amounts and formulations of the compounds can be added to determine the effects on the screening assay.

In one aspect of the present invention, compounds that attenuate or inhibit an inflammatory response of a cell to glycated albumin are used as therapeutic agents. One skilled in the art knows how to measure cytokine expression. The amount and type of cytokine expressed can be determined using immunological methods, such as ELISA assays. The methods of the present invention are not limited by the type of assay used to measure the amount of cytokine expressed, and any methods known to those skilled in the art and later developed can be used to measure the amount of cytokines expressed in response to the stimulating agent and to the compound having an unknown effect.

CORRELATION OF PHYSIOLOGICAL PARAMETERS AND ASSAYS TO DISEASES AND CONDITIONS

Tables 9-12 provide disclosure and references that link or relate the various parameters and assays disclosed herein to general and/or specific conditions or diseases. The references provided in these tables support the specification as fully enabled for treating all the diseases or conditions encompassed herein, based on the inhibiting effect of the compounds provided in the specification, and the predictive nature of the tests provided of the disclosed uses.

Table 9 provides references illustrating the connection between TNF-α and IL-6 in rheumatoid arthritis, vascular inflammation, and atherosclerosis.

Table 10 provides references illustrating the importance of HSPG expression in the prevention of atherosclerosis and diabetic vascular disease.

Table 11 provides references illustrating the role of SMC proliferation in contributing to restenosis and atherosclerosis.

Table 12 provides references illustrating the role of heparanase and TNF-α expression in promoting tumor angiogenesis and metastasis, as well as the use of inhibitors of heparanase and TNF-α expression in treating cancer.

Examples of assays described herein for screening the compounds of the present invention include, but are not limited to, assays that demonstrate: a) inhibition of SMC proliferation, that was used to identify, for example, compounds in Table 5; b) induction of HSPG expression in SMCs; c) induction of heparanase expression in endothelial cells; d) inhibition of AGE-induced inflammatory response in endothelial cells as measured by IL-6 or other inflammatory cytokine expression, that was used to identify, for example, compounds in Table 8; and e) cytotoxicity effects of the disclosed compounds. By using these disclosed assays, the present disclosure is fully enabled for identification of compounds for the treatment or prevention of the diseases disclosed generically or specifically.

Table 9. The Role of TNF-α, IL-6, and AGE in Rheumatoid Arthritis, Vascular Inflammation, and Atherosclerosis.

Author	*Title of Reference*	*Reference Citation*	*Physiological Parameter*	*Disease*
Feldmann M Ref 1	Discovery of TNF-α as a therapeutic target in rheumatoid arthritis: preclinical and clinical studies	Joint Bone Spine. 2002 Jan;69(1):12-8 Review	TNF inhibition	Arthritis
Choy et al Ref 2	Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial.	Arthritis Rheum. 2002 Dec;46(12):3143-50	IL-6 inhibition	Arthritis
Wong et al Ref 3	The role of the interleukin-6 family of cytokines in inflammatory arthritis and bone turnover	Arthritis Rheum. 2003 May;48(5):1177-89. Review	IL-6 inhibition	Arthrits
Basta et al Ref 4	Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes	Cardiovasc Res. 2004 Sep 1;63(4):582-92	AGE-IL6 inhibition	Diabetic vascular diseases

Table 10. The Role of HSPG Induction in the Prevention of Atherosclerosis and Diabetic Vascular Disease.

Author	*Title of Reference*	*Reference Citation*	*Physiological Parameter*	*Disease*
Engelberg H. Ref 5	Endogenous heparin activity deficiency: the 'missing link' in atherogenesis?	Atherosclerosis. 2001 Dec;159(2):253-60. Review	HSPG induction	Atherosclerosis
Jensen T Ref 6	Pathogenesis of diabetic vascular disease: evidence for the role of reduced heparan sulfate proteoglycan	Diabetes. 1997 Sep;46 Suppl 2:S98-100	HSPG induction	Diabetic vascular disease
Hollmann J et al, Ref 7	Relationship of sulfated glycosaminoglycans and cholesterol content in normal and atherosclerotic human aorta	Artherosclerosis. 1989;9:154–8	HSPG	Atherosclerosis
Kruse R et al Ref 8	Cholesterol-dependent changes of glycosaminoglycan pattern in human aorta	Basic Res Cardiol. 1996 Sep-Oct;91(5):344-52	HSPG	Atherosclerosis

Table 11. The Role of SMC Proliferation in Restenosis and Atherosclerosis.

Author	*Title of Reference*	*Reference Citation*	*Physiological Parameter*	*Disease*
Chen et al Ref 9	Electron microscopic studies of phenotypic modulation of smooth muscle cells in coronary arteries of patients with unstable angina pectoris and postangioplasty restenosis	Circulation. 1997 Mar 4;95(5):1169-75	Smooth muscle cell (SMC) proliferation	Restenosis
Braun-Dullaeus et al Ref 10	Cell cycle progression: new therapeutic target for vascular proliferative disease	Circulation. 1998 Jul 7;98(1):82-9	Smooth muscle cell (SMC) proliferation	Restenosis
Boucher et al Ref 11	LRP: role in vascular wall integrity and protection from atherosclerosis	Science. 2003 Apr 11;300(5617):329-32	Smooth muscle cell (SMC) proliferation	Atherosclerosis
Marx et al Ref 12	Bench to bedside: the development of rapamycin and its application to stent restenosis	Circulation. 2001 Aug 21;104(8):852-5	Smooth muscle cell (SMC) proliferation	Restenosis

Table 12. The Role of Heparanase and TNF-α in Promoting Tumor Angiogenesis and Metastasis and the Use of Heparanase and TNF-α Inhibitors in Treating Cancer.

Author	*Title of Reference*	*Reference Citation*	*Physiological Parameter*
Vlodavsky I et al Ref 13	Molecular properties and involvement of heparanase in cancer metastasis and angiogenesis	J Clin Invest. 2001 Aug;108(3):341-7. Review	Heparanase inhibition
Goldshmidt et al Ref 14	Cell surface expression and secretion of heparanase markedly promote tumor angiogenesis and metastasis	Proc Natl Acad Sci U S A. 2002 Jul 23;99(15):10031-6	Heparanase inhibition
Simizu et al Ref 15	Heparanase as a molecular target of cancer chemotherapy	Cancer Sci. 2004 Jul;95(7):553-8	Heparanase inhibition
Szlosarek et al Ref 16	Tumour necrosis factor α: a potential target for the therapy of solid tumours	The Lancet Oncology 2003 Sept; 4:565-73	TNFα inhibition

COMPOUND/COMPOSITION-COATED MEDICAL DEVICES

The compounds of the present invention can be used alone, in various combinations with one another, and/or in combination with other agents along with delivery devices to effectively prevent and treat the diseases described herein, though particular applications are found in vascular disease, and in particular, vascular disease caused by injury and/or by transplantation. Though this example focuses on vascular disease, provision of the compounds of the present invention with medical devices for treatment of the diseases and conditions capable of being treated with the compounds is contemplated by the present invention.

Various medical treatment devices utilized in the treatment of vascular disease may ultimately induce further complications. For example, balloon angioplasty is a procedure utilized to increase blood flow through an artery and is the predominant treatment for coronary vessel stenosis. However, the procedure typically causes a certain degree of damage to the vessel wall, thereby creating new problems or exacerbating the original problem at a point later in time. Although other procedures and diseases may cause similar injury, exemplary aspects of the present invention will be described with respect to the treatment of restenosis and related complications following percutaneous transluminal coronary angioplasty and other similar arterial/venous procedures, including the joining of arteries, veins, and other fluid carrying conduits in other organs or sites of the body, such as the liver, lung, bladder, kidney, brain, prostate, neck, and legs.

The local delivery of a compound of the present invention and, in some aspects, along with other therapeutic agents, from a stent prevents vessel recoil and remodeling through the scaffolding action of the stent. The effect of a compound provided, with or without other therapeutic agents, helps determine the particular application for which the coated medical device is being administered. For example, compound-coated stents can prevent multiple components of neointimal hyperplasia or restenosis as well as reduce inflammation and thrombosis. Local administration of a compound of the present invention and other therapeutic agents to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations of the compounds of the present invention and other therapeutic agents

can be achieved utilizing local delivery rather than systemic administration. In addition, reduced systemic toxicity can be achieved utilizing local delivery rather than systemic administration while maintaining higher tissue concentrations. In utilizing local delivery from a stent rather than systemic administration, a single procedure may suffice with better patient compliance. An additional benefit of combination therapeutic agent and/or compound therapy can be to reduce the dose of each of the therapeutic agents, thereby limiting toxicity, while still achieving a reduction in restenosis, inflammation, and thrombosis. Local stent-based therapy is therefore a means of improving the therapeutic ratio (efficacy/toxicity) of anti-restenosis, anti-inflammatory, and anti-thrombotic therapeutic agents.

Although exemplary aspects of the invention will be described with respect to the treatment of restenosis and other related complications, it is important to note that the local delivery of a compound of the present invention, alone or as part of a therapeutic agent combination, can be utilized to treat a wide variety of conditions utilizing any number of medical devices, or to enhance the function and/or life of the device. For example, intraocular lenses, placed to restore vision after cataract surgery, are often compromised by the formation of a secondary cataract. The latter is often a result of cellular overgrowth on the lens surface and can be potentially minimized by combining one or more compounds of the present invention having an effect in preventing unwanted cellular growth with the device. Other medical devices that often fail due to tissue in-growth or accumulation of proteinaceous material in, on and around the device, such as shunts for hydrocephalus, dialysis grafts, colostomy bag attachment devices, ear drainage tubes, leads for pace makers, and implantable defibrillators can also benefit from the combinations of the compounds of the present invention, possibly other pharmaceutical agents, and the devices. Other surgical devices, sutures, staples, anastornosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular implants, tissue adhesives and sealants, tissue scaffolds, various types of dressings, bone substitutes, intraluminal devices, and vascular supports could also provide enhanced patient benefit using this compound-device combination approach. Essentially, any type of medical device can be coated in some fashion with at least one compound of the

present invention, alone or as part of a therapeutic agent combination, which enhances treatment over the use of the device or therapeutic agent without combination with the compound.

As disclosed supra, the compounds of the present invention can be administered in combinational therapies with other therapeutic agents, and are not limited to only the other therapeutic agents disclosed herein. Thus, the present invention also contemplates, in addition to various medical devices, the coatings on these devices can be used to deliver a compound of the present invention in combination with other therapeutic agents. This illustrative list of therapeutic agents can be administered through pharmeutical means or in association with medical devices and such therapeutic agents include, but are not limited to, antiproliferative/antimitotic agents including natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (e.g., etoposide, teniposide), antibiotics [e.g., dactinomycin (actinomycin D) daunorubicin, doxorubicin, and idarubicin], anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents such as G(GP) IIb/IIIa inhibitors and vitronectin receptor antagonists; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nirtosoureas [carmustine (BCNU) and analogs, streptozocin], trazenes-dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (e.g., fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors [mercaptopurine, thioguanine, pentostatin, and 2-chlorodeoxyadenosine (cladribine)]; platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (e.g., estrogen); anticoagulants (e.g., heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase, and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory; antisecretory (breveldin); anti-

inflammatory agents such as adrenocortical steroids (e.g., cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6α-methylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives, i.e., aspirin; para-aminophenol derivatives, i.e., acetominophen; indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressives, (Cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); angiogenic agents: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); angiotensin receptor blockers; nitric oxide donors; anti-sense oligionucleotides and combinations thereof; cell cycle inhibitors, mTOR inhibitors, and growth factor signal transduction kinase inhibitors.

Although any number of stents can be utilized in accordance with the present invention, for simplicity, a limited number of stents will be described in exemplary aspects of the present invention. The skilled artisan will recognize that any number of stents can be utilized in connection with the present invention. In addition, as stated above, other medical devices can be utilized. For example, though stents are described, sleeves outside the vessels are also contemplated, as are other medical devices that can provide a substrate for administration for at least one of the compounds of the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Typically, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device *in situ*. A common method of expansion occurs through the use of a catheter-mounted, angioplasty balloon that is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen.

A stent may resemble an expandable cylinder and may comprise a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or

lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent can be expanded circumferentially and maintained in an expanded configuration that is circumferentially or radially rigid. The stent can be axially flexible and when flexed at a band, for example, the stent avoids any externally protruding component parts.

The stent can be fabricated utilizing any number of methods. For example, the stent can be fabricated from a hollow or formed stainless steel tube that can be machined using lasers, electric discharge milling, chemical etching or other means. The stent is inserted into the body and placed at the desired site in an unexpanded form. In one aspect, expansion can be effected in a blood vessel by a balloon catheter, where the final diameter of the stent is a function of the diameter of the balloon catheter used. It should be appreciated that a stent in accordance with the present invention can be embodied in a shape-memory material including, for example, an appropriate alloy of nickel and titanium or stainless steel.

Structures formed from stainless steel can be made self-expanding by configuring the stainless steel in a predetermined manner, for example, by twisting it into a braided configuration. In this aspect, after the stent has been formed it can be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. Upon emerging from the catheter, the stent can be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature, or electrical stimulation.

Furthermore, a stent can be modified to comprise one or more reservoirs. Each of the reservoirs can be opened or closed as desired. These reservoirs can be specifically designed to hold the the compound or compound/therapeutic agent combination to be delivered. Regardless of the design of the stent, it is preferable to have the compound or compound/therapeutic agent combination dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the affected area. In this regard, the reservoir size in the bands is preferably sized to adequately apply the compound or compound/therapeutic agent combination dosage at the desired location and in the desired amount.

In an alternative aspect, the entire inner and outer surface of the stent can be coated with the compound or compound/therapeutic agent combination in therapeutic dosage amounts. The coating techniques may vary depending on the the compound or compound/therapeutic agent combination. Also, the coating techniques may vary depending on the material comprising the stent or other intraluminal medical device.

One or more compounds of the present invention and, in some instances, other therapeutic agents as a combination, can be incorporated onto or affixed to the stent in a number of ways. In one aspect, the compound is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The compound elutes from the polymeric matrix over time and enters the surrounding tissue. The compound preferably remains on the stent for at least three days up to approximately six months, and more preferably between seven and thirty days.

Any number of non-erodible polymers can be utilized in conjunction with the compound, and such polymeric compositions are well known in the art. In one aspect, the polymeric matrix comprises two layers. The base layer comprises a solution of poly(ethylene-co-vinylacetate) and polybutylmethacrylate. The compound is incorporated into this base layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the compound from eluting too quickly. The thickness of the outer layer or topcoat determines the rate at which the compound elutes from the matrix. Essentially, the compound elutes from the matrix by diffusion through the polymer matrix. Polymers are permeable, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about one micron to about twenty microns or greater. It is important to note that primer layers and metal surface treatments can be utilized before the polymeric matrix is affixed to the medical device. For example, acid cleaning, alkaline (base) cleaning, salinization and parylene deposition can be used as part of the overall process described above.

The poly(ethylene-co-vinylacetate), polybutylmethacrylate, and compound solution can be incorporated into or onto the stent in a number of ways. For example, the solution can be sprayed onto the stent or the stent can be dipped into the solution. Other methods include spin coating and plasma polymerization. In one aspect, the

solution is sprayed onto the stent and then allowed to dry. In another aspect, the solution can be electrically charged to one polarity and the stent electrically charged to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste can be reduced and more precise control over the thickness of the coat can be achieved.

Drug-coated stents are manufactured by a number of companies including Johnson & Johnson, Inc. (New Brunswick, NJ), Guidant Corp. (Santa Clara, CA), Medtronic, Inc. (Minneapolis, MN), Cook Group Incorporated (Bloomington, IN), Abbott Labs., Inc. (Abbott Park, IL), and Boston Scientific Corp. (Natick, MA). *See e.g.,* U.S. Patent No. 6,273, 913; U.S. Patent Application Publication No. 20020051730; WO 02/26271; and WO 02/26139.

PHARMACEUTICAL COMPOSITIONS

In one aspect, the present invention provides a composition comprising at least one compound as disclosed herein.

In another aspect, this invention provides a pharmaceutical composition, comprising:

at least one compound as disclosed herein; and

optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof.

In yet another aspect, this invention provides a pharmaceutical composition, comprising:

at least one compound as disclosed herein; and

optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof;

wherein the pharmaceutical composition is in the form of a tablet, a capsule, a syrup, a cachet, a powder, a granule, a solution, a suspension, an emulsion, a bolus, a lozenge, a suppository, a cream, a gel, a paste, a foam, a spray, an aerosol, a microcapsule, a liposome, or a transdermal patch.

In still another aspect, this invention provides a pharmaceutical composition, comprising:

at least one compound as disclosed herein;

optionally comprising a pharmaceutically acceptable additive selected from a carrier, an auxiliary, a diluent, an excipient, a preservative, a solvate, or any combination thereof; and

further comprising an agent selected from a chemotherapeutic agent, an immunosuppressive agent, a cytokine, a cytotoxic agent, an anti-inflammatory agent, an antirheumatic agent, an antidyspilidemic agent, a cardiovascular agent, or any combination thereof.

Accordingly, in addition to the compounds disclosed herein, the pharmaceutical compositions of the present invention can further comprise at least one of any suitable auxiliary such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant, or the like. In one aspect of the present invention, pharmaceutically acceptable auxiliaries are employed. Examples and methods of preparing such sterile solutions are well known in the art and can be found in well known texts such as, but not limited to, REMINGTON'S PHARMACEUTICAL SCIENCES (Gennaro, Ed., 18th Edition, Mack Publishing Co. (1990)). Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the compound.

PHARMACEUTICAL COMPOSITIONS FOR ORAL ADMINISTRATION

For oral administration in the form of a tablet or capsule, a compound can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents may also be incorporated into the mixture. Suitable binders include, without limitation, starch; gelatin; natural sugars such as glucose or beta-lactose; corn sweeteners; natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose; polyethylene glycol; waxes; and the like. Lubricants used in these dosage forms include, without limitation, sodium oleate, sodium stearate,

magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Formulations of the present invention suitable for oral administration can be presented as discrete units such as capsules, cachets, or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, and the like.

ROUTES OF ADMINISTRATION

The invention further relates to the administration of at least one compound disclosed herein by the following routes, including, but not limited to oral, parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, iontophoretic means, or transdermal means.

DOSAGES

A composition comprising at least one compound of the present invention can be administered at a frequency and for a period of time effective to achieve a therapeutic effect, which should be understood in the context of a regimen of repeated administration at such a frequency and over such a period. In some aspects, a composition is administered at a frequency and for a period of time effective to increase a HSPG expression. In some aspects, a composition can be administered in a single daily dose, or a total daily dosage can be administered in divided doses of two, three, or four times daily. Typically and most conveniently, a composition is administered at least once daily, but in certain situations less frequent, *e.g.*, twice weekly or weekly, administration can be effective. For greatest benefit,

administration should continue for a prolonged period, for example at least about 3 months, or at least about 6 months, or at least about 1 year, or at least about 2 years, or at least about 3 years. In one aspect, administration continues from a time of initiation for substantially the remainder of the mammal's life.

The selection and/or amounts of individual compounds can, if desired vary over the period of administration. In one aspect, a single composition of this invention is administered to a mammal for the entire period of administration. In other aspects, different compositions comprising at least one compound are administered to the mammal at different times.

The dosages of compounds can be adjusted on a per body weight basis and may thus be suitable for any subject regardless of the subject's size.

In one aspect of this invention, daily oral dose comprises a total compound amount of at least about 0.0001 mg per kg body weight, illustratively about 0.0001 mg to about 1000 mg, about 0.001 mg to about 100 mg, about 0.01 mg to about 10 mg, about 0.1 mg to about 5 mg, or about 1 to about 3 mg per kg body weight.

In another aspect, a daily intravenous injection comprises a total compound amount of at least about 0.0001 mg per kg body weight, illustratively about 0.0001 mg to about 0.5 mg, about 0.001 mg to about 0.25, or about 0.01 to about 0.03 mg per kg body weight.

Illustratively, a tablet for oral administration can be manufactured to comprise a total compound amount of about 0.001 mg, about 0.1 mg, about 0.2 mg, about 0.5 mg, about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 15 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg.

In one aspect, a composition comprises an active ingredient content of at least about 0.01% by weight of the composition, illustratively about 0.01% to about 99%, about 0.05% to about 90%, about 0.1% to about 80%, about 0.5% to about 50% by weight of the composition. The amount of active ingredient that can be combined with other materials to produce a single dosage form varies depending upon the subject treated and the particular mode of administration.

An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.1 mg/kg to about 20 mg/kg of body weight per day. In one aspect, the range is from about 0.2 mg/kg to about 10 mg/kg of body weight per day. In another aspect, the range is from about 0.5 mg/kg to about 10 mg/kg of body weight per day. The compounds can be administered on a regimen of about 1 to about 10 times per day.

Co-administration or sequential administration of the compounds of the present invention and other therapeutic agents can be employed, such as chemotherapeutic agents, immunosuppressive agents, cytokines, cytotoxic agents, nucleolytic compounds, radioactive isotopes, receptors, and pro-drug activating enzymes, which can be naturally occurring or produced by recombinant methods. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active therapeutic agents simultaneously exert their biological activities.

It is to be understood that this invention is not limited to the particular methodology, syntheses, formulations, protocols, cell lines, constructs, and reagents described herein and as such can vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to limit the scope of the present invention.

All publications, patents, and other references mentioned herein are provided for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in these references, which might be used in connection with the presently described invention.

DEFINITIONS AND TERMINOLOGY

The groups defined for various symbols used in the formulas of this disclosure, as well as the optional substituents defined on those groups, can be defined as follows. Unless otherwise specified, any recitation of the number of carbon atoms in a particular group is intended to refer to the unsubstituted "base" group, therefore, any substituent recited on a base group is described by its own definition, including its

own limitation of the number of carbon atoms. Unless otherwise specified, all structural isomers of a given structure, for example, all enantiomers, diasteriomers, and regioisomers, are included within this definition.

The terms 'halogen' or 'halo' includes fluorine, chlorine, bromine, or iodine.

The term 'alkyl' group is used to refer to both linear and branched alkyl groups. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, pentyl, hexyl, heptyl, octyl, nonyl, or decyl, and the like. Unless otherwise specified, an alkyl group has from 1 to 10 carbon atoms. Also unless otherwise specified, all structural isomers of a given structure, for example, all enantiomers and all diasteriomers, are included within this definition. For example, unless otherwise specified, the term propyl is meant to include *n*-propyl and *iso*-propyl, while the term butyl is meant to include *n*-butyl, *iso*-butyl, *t*-butyl, *sec*-butyl, and so forth.

'Haloalkyl' is a group containing at least one halogen and an alkyl portion as define above. Unless otherwise specified, all structural isomers of a given structure, for example, all enantiomers and all diasteriomers, are included within this definition. Exemplary haloalkyl groups include fluoromethyl, chloromethyl, fluoroethyl, chloroethyl, trilfluoromethyl, and the like. Unless otherwise specified, a haloalkyl group has from 1 to 10 carbon atoms.

A 'cycloalkyl' group refers to a cyclic alkyl group which can be mono or polycyclic. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl. Unless otherwise specified, a cycloalkyl group has from 3 to 10 carbon atoms.

'Alkoxy' refers to an -O(alkyl) group, where alkyl is as defined above. Therefore, unless otherwise specified, all isomers of a given structure are included within a definition. Exemplary alkyl groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *t*-butoxy, and the like. Unless otherwise specified, an alkoxy group has from 1 to 10 carbon atoms.

'Haloalkoxy' is an alkoxy group with a halo substituent, where alkoxy and halo groups are as defined above. Exemplary haloalkoxy groups include chloromethoxy, trichloroethoxy, trifloroethoxy, perfluoroethoxy ($-OCF_2CF_3$),

trifluoro-*t*-butoxy, hexafluoro-*t*-butoxy, perfluoro-*t*-butoxy (-$OC(CF_3)_3$), and the like. Unless otherwise specified, an haloalkoxy group typically has from 1 to 10 carbon atoms.

'Alkylthio' refers to an -S(alkyl) goup, where alkyl group is as defined above. Exemplary alkyl groups include methylthio, ethylthio, propylthio, butylthio, *iso*-propylthio, *iso*-butylthio, and the like. Unless otherwise specified, an alkylthio group typically has from 1 to 10 carbon atoms.

'Aryl' is optionally substituted monocylic or polycyclic aromatic ring system of 6 to 14 carbon atoms. Exemplary groups include phenyl, naphthyl and the like. Unless otherwise specified, an aryl group typically has from 6 to 14 carbon atoms.

'Heteroaryl' is an aromatic monocyclic or polycyclic ring system of 4 to 10 carbon atoms, having at least one heteroatom or heterogroup selected from -O-, >N-, -S-, >NH or NR, and the like, wherein R is a substituted or unsubstituted alkyl, aryl, or acyl, as defined herein. In this aspect, >NH or NR are considered to be included when the heteroatom or heterogroup can be >N-. Exemplary heteroaryl groups include as pyrazinyl, isothiazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyridazinyl, thienopyrimidyl, furanyl, indolyl, isoindolyl, benzo[1,3]dioxolyl, 1,3-benzoxathiole, quinazolinyl, pyridyl, thiophenyl and the like. Unless otherwise specified, a heteroaryl group typically has from 4 to 10 carbon atoms. Moreover, the heteroaryl group can be bonded to the heterocyclic core structure at a ring carbon atom, or, if applicable for a *N*-substituted heteroaryl such as pyrrole, can be bonded to the heterocyclic core structure through the heteroatom that is formally deprotonated to form a direct heteroatom-pyrimdine ring bond.

'Heterocyclyl' is a non-aromatic saturated monocyclic or polycyclic ring system of 3 to 10 member having at least one heteroatom or heterogroup selected from -O-, >N-, -S-, >NR, $>SO_2$, >CO, and the like, wherein R is hydrogen or a substituted or an unstubstituted alkyl, aryl, or acyl, as defined herein. Exemplary heterocyclyl groups include aziridinyl, pyrrolidinyl, piperdinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl and the like. Unless otherwise specified, a heterocyclyl group typically has from 2 to 10 carbon atoms. A heterocyclyl group can be bonded through a heteroatom that is formally deprotonated

or a heterocyclyl group can be bonded through a carbon atom of the heterocyclyl group.

Further, the meaning of certain additional terms and phrases employed in the specification, can be defined as follows.

As used herein, the term "compound" includes both the singular and the plural, and includes any single entity or combined entities that have at least the affect disclosed herein and combinations, fragments, analogs or derivatives of such entities.

As used herein, the term "substance" refers broadly to any material of a particular kind or constitution. Examples of a "substance" can include, without limitation, a chemical element, a molecule, a compound, a mixture, a composition, an emulsion, a chemotherapeutic agent, a pharmacological agent, a hormone, an antibody, a growth factor, a cellular factor, a nucleic acid, a protein, a peptide, a peptidomimetic, a nucleotide, a carbohydrate, and combinations, fragments, analogs or derivatives of such entities.

The term "glycated protein," as used herein, includes proteins linked to glucose, either enzymatically or non-enzymatically, primarily by condensation of free epsilon-amino groups in the protein with glucose, forming Amadori adducts. Furthermore, glycated protein, as used herein, includes not only proteins containing these initial glycation products, but also glycation products resulting from further reactions such as rearrangements, dehydration, and condensations that form irreversible advanced glycation end products (AGE).

The terms "treatment", "treating", "treat", and the like are used herein to refer generally to any process, application, therapy, etc., wherein a mammal is subject to medical attention with the object of obtaining a desired pharmacological and/or physiological effect for improving the mammal's condition or disease, directly or indirectly. The effect can be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. The effect also can include, for example, inhibition of disease symptom (*i.e.*, arresting its development) or relieving disease symptom (*i.e.*, causing regression of the disease or symptom).

A used herein, the term "therapeutically-effective amount" refers to that amount of at least one compound as disclosed herein, or their pharmaceutically-acceptable salts thereof, that is sufficient to bring about the biological or medical effect that is being sought in a mammal, system, tissue, or cell.

The term “preventing”, “prevent”, “prevention”, and the like are used herein to refer generally to any process, application, therapy, etc., wherein a mammal is subject to medical attention with the object of obtaining a desired pharmacological and/or physiological effect for preventing onset of clinically evident condition or disease or preventing onset of a preclinically evident stage of a condition or disease. The effect can be prophylactic in terms of completely or partially preventing or reducing the risk of occurance of a condition or disease or symptom thereof.

A used herein, the term "prophylactically-effective amount" refers to that amount of a drug or pharmaceutical agent that will prevent or reduce the risk of occurrence of the biological or medical effect that is sought to be prevented in the cell, tissue, system, or mammal.

As used herein, the term “activation” refers to any alteration of a signaling pathway or biological response including, for example, increases above basal levels, restoration to basal levels from an inhibited state, and stimulation of the pathway above basal levels.

Publications and patents mentioned herein are disclosed for the purpose of describing, for example, the constructs and methodologies that are provided in the publications and patents, which might be used in connection with the present invention. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such publications, patents, or other disclosure by virtue of prior invention.

To the extent that any definition or usage provided by any document incorporated herein by reference conflicts with the definition or usage provided herein, the definition or usage provided herein controls.

For any particular compound disclosed herein, any general structure presented also encompasses all conformational isomers, regioisomers, stereoisomers and tautomers that can arise from a particular set of substituents. The general structure also encompasses all enantiomers, diastereomers, and other optical isomers whether in enantiomeric or racemic forms, as well as mixtures of stereoisomers, as the context requires. The general structure also encompasses all salts, including pharmaceutically acceptable and non-pharmaceutically acceptable salts and prodrugs thereof.

When Applicants disclose or claim a range of any type, for example a range of temperatures, a range of numbers of atoms, a molar ratio, or the like, Applicants' intent is to disclose or claim individually each possible number that such a range could reasonably encompass, as well as any sub-ranges and combinations of sub-ranges encompassed therein. For example, when the Applicants disclose or claim a chemical moiety having a certain number of carbon atoms, Applicants' intent is to disclose or claim individually every possible number that such a range could encompass, consistent with the disclosure herein. For example, the disclosure that R is selected independently from an alkyl group having up to 20 carbon atoms, or in alternative language a C_1 to C_{20} alkyl group, as used herein, refers to an R group that can be selected independently from a hydrocarbyl group having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms, as well as any range between these two numbers for example a C_3 to C_8 alkyl group, and also including any combination of ranges between these two numbers for example a C_3 to C_5 and C_7 to C_{10} hydrocarbyl group. In another example, by the disclosure that the molar ratio typically spans the range from about 0.1 to about 1.1, Applicants intend to recite that the molar ratio can be selected from about 0.1:1, about 0.2:1, about 0.3:1, about 0.4:1, about 0.5:1, about 0.6:1, about 0.7:1, about 0.8:1, about 0.9:1, about 1.0:1, or about 1.1:1.

Applicants reserve the right to proviso out or exclude any individual members of any such group, including any sub-ranges or combinations of sub-ranges within the group, that may be claimed according to a range or in any similar manner, if for any reason Applicants choose to claim less than the full measure of the disclosure, for example, to account for a reference that Applicants may be unaware of at the time of

the filing of the application. Further, Applicants reserve the right to proviso out or exclude any individual substituents, compounds, ligands, structures, or groups thereof, or any members of a claimed group, if for any reason Applicants choose to claim less than the full measure of the disclosure, for example, to account for a reference that Applicants may be unaware of at the time of the filing of the application.

The following references disclose certain heterocyclic compounds.

Table X References disclosing heterocyclic compounds.

Publication or Patent No.	Title
US 6,476,031	Quinazoline Derivatives as Medicaments
US 6,335,446	Quinolinium- and Pyridinium-Based Fluorescent Dye Compounds
US 5,753,675	Quinoline Analogs of Mevalonolactone and Derivates Thereof
US 5,739,127	2,4'-Bridged Bis-2,4-Diaminoquinazolines
US 5,064,833	Substituted Quinazoline Derivates for Use in Gastrointestinal Diseases
US 4,923,861	6-(2-(2-(Substituted Amino)-3-Quinolinyl) Ethenyl and Ethyl) Tetrahydro-4-Hydroxypyran-2-One Inhibitors of Cholesterol Biosynthesis
WO 2005/076861	Compounds that Inhibit HIV Particle Formation
WO 2005/054236	Substituted Quinolines for the Treatment of Cancer
WO 2005/046698	Fused Heterocyclic Compounds
WO 2005/030129	Quinoline Potassium Channel Inhibitors
WO 2005/000285	Methods of Treating Non-Inflammatory Gastrointestinal Tract Disorders Using $Ca_v2.2$ Subunit Calcium Channel Modulators
WO 2004/081009	Quinaoline Derivatives as TGF-Beta Inhibitors
WO 2004/080444	Methods for Treating Lower Urinary Tract Disorders and the Related Disorders Vul-Vodynia and Vulvar Vestibulitis Using $Ca_v2.2$ Subunit Calcium Channel Modulators
WO 2004/078733	Quinazolines Useful as Modulators of Ion Channels
WO 2004/013091	4-Anilido Substituted Quinazolines and Use Thereof as Inhibitors of Epidermal Growth Factor Receptor Kinases

WO 2004/010929	Methods for Improvement of Lung Function Using TGF-β Inhibitors
WO 2003/097615	Treatment of Fibroproliferative Disorders Using TGF-β Inhibitors
WO 2003/018561	N-Type Calcium Channel Antagonists for the Treatment of Pain
WO 2003/016292	Ultraviolet Light Absorbers
WO 2002/030888	Tricyclic Compounds and Uses Thereof
WO 2001/032632	Pharmaceutical Compounds
WO 2000/076982	Antagonism of Immunostimulatory CPG-Oligonucleotides by 4-Aminoquinolines and other Weak Bases
WO 2000/001696	3-Alkylpyrrolo[3,2-c]quinoline Derivatives
WO 9918077	Fused Pyridine Derivatives
WO 9818764	Dihydrobenzoanthracenone, -Pyrimidinone or Dihydronaphtoquinolinone
WO 9720822	Quinazolin-2,4-Diazirines as NPY Receptor Antagonist
WO 9720821	Heteroaryl Derivatives
WO 9618615	Polyarylcarbamoylaza -and-Carbamoylalkanedioic Acids
WO 9303030	Quinoline Derivatives as Immunostimulants
WO 9218123	A Method for Inhibition of Retroviral Replication
WO 8905297	Compounds
DE 2314985	(German translation)
DE 19651099	(German translation)
DE 19615262 (US 6,329,360)	Hetero-Linked Phenylglycinolamides
DE 1935382 (US 3,637,693)	Hydroxyarylquinazolines and Their Use as UV-Absorbers
EP 579496	4-Aminoquinazoline Derivatives, and Their Use as Medicine
EP 535548	Inhibitor of Atherosclerotic Intimal Thickening
EP 491441	Fungicidal Isoquinoline Derivatives
EP 453197	Amine Derivatives
EP 304063	Quinoline Type Mevalonolactones
JP 10308277	Organic Electroluminescent Element
JP 06263744	Production of 2,4-Diaminoquinazolines

JP 06116239	7-Substituted-3,5-Dihydroxyhept-6-Ynoic Acid Compounds
JP 06041114	New Mevalonolactones and Its Production
JP 05310700 (WO 09511898)	Condensed Pyridine-Based Mevalonolactone Intermediate and Its Production

Applicants reserve the right to proviso out or to restrict from any claim currently presented, or from any claim that may be presented in this or any further application based upon this disclosure, including claims drawn any genus or subgenus disclosed herein, any compound or group of compounds disclosed in any reference, including any reference provided herein.

The following acronyms, abbreviations, terms and definitions have been used throughout this disclosure. The following acronyms, abbreviations, terms and definitions have been used throughout the experimental section. **Acronyms and abbreviations:** THF (tetrahydrofuran), K_2CO_3 (potassium carbonate), n-BuLi (n-butyllithium), DMF (*N,N*-dimethylformamide, *i*-PrOH or IPA (iso-propanol), NaCl (sodium chloride), NaH (sodium hydride), EtOAc (ethyl acetate), g (grams), mL (milliliters), mp (melting point), rt or RT (room temperature), aq (aqueous), min (minute), h or hr (hour), atm (atmosphere), conc. (concentrated), MS or mass spec (mass spectroscopy/spectrometry), NMR (nuclear magnetic resonance). **NMR abbreviations:** br (broad), apt (apparent), s (singlet), d (doublet), t (triplet), q (quartet), dq (doublet of quartets), dd (doublet of doublets), dt (doublet of triplets), m (multiplet).

General Synthetic Procedures.

Room temperature is defined as an ambient temperature range, typically from about 20°C to about 35°C. An ice bath (crushed ice and water) temperature is defined as a range, typically from about –5°C to about 0 °C. Temperature at reflux is defined as ±15°C of the boiling point of the primary reaction solvent. Overnight is defined as a time range of from about 8 to about 16 hours. Vacuum filtration (water aspirator) is defined as occurring over a range of pressures, typically from about 5 mm Hg to about 15 mm Hg. Dried under vacuum is defined as using a high vacuum pump at a range

of pressures, typically from about 0.1 mm Hg to about 5 mm Hg. Neutralization is defined as a typical acid-based neutralization method and measured to a pH range of from about pH 6 to about pH 8, using pH-indicating paper. Brine is defined as a saturated aqueous sodium chloride. Nitrogen atmosphere is defined as positive static pressure of nitrogen gas passed through a Drierite™ column with an oil bubbler system. Concentrated ammonium hydroxide is defined as an approximately 15 M solution. Melting points were measured against a mercury thermometer and are not corrected.

All eluents for column or thin layer chromatography were prepared and reported as volume:volume (v:v) solutions. The solvents, reagents, and the quantities of solvents and/or reagents used for reaction work-up or product isolation can be those that typically would be used by one of ordinary skill in organic chemical synthesis, as would be determined for the specific reaction or product to be isolated. For example: 1) crushed ice quantity typically ranged from about 10 g to about 1000 g depending on reaction scale; 2) silica gel quantity used in column chromatography depended on material quantity, complexity of mixture, and size of chromatography column employed and typically ranged from about 5 g to about 1000 g; 3) extraction solvent volume typically ranged from about 10 mL to about 500 mL, depending upon the reaction size; 4) washes employed in compound isolation ranged from about 10 mL to about 100 mL of solvent or aqueous reagent, depending on scale of reaction; and 5) drying reagents (potassium carbonate, sodium carbonate or magnesium sulfate) ranged from about 5 g to about 100 g depending on the amount of solvent to be dried and its water content.

Spectroscopic and other Instrumental Procedures

NMR. The ^{1}H spectra described herein were obtained using Varian Gemini 200 MHz spectrometers. Spectrometer field strength and NMR solvent used for a particular sample are indicated in the examples, or on any NMR spectra that are shown as Figures. Typically, ^{1}H NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from tetramethylsilane (TMS) (δ = 0 ppm) as an internal standard. Solid or liquid samples were dissolved in an appropriate NMR

solvent (typically $CDCl_3$ or DMSO-d_6), placed in a NMR sample tube, and data were collected according to the spectrometer instructional manuals. Most samples were analyzed in Variable Temperature mode, typically at about 55 °C, though some data for some samples were collected with the probe at ambient probe temperature. NMR data were processed using the software provided by Varian, VNMR 6.1 G version.

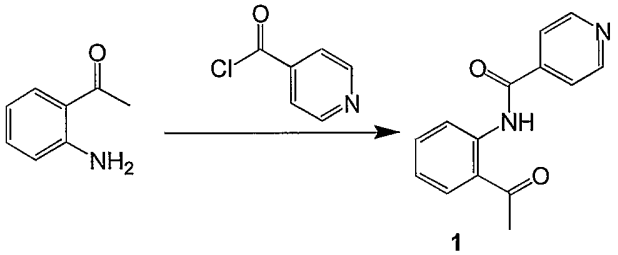
The present invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope of this disclosure, but rather are intended to be illustrative only. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to one of ordinary skill in the art without departing from the spirit of the present invention. Thus, the skilled artisan will appreciate how the experiments and Examples may be further implemented as disclosed by variously altering the following examples, substituents, reagents, or conditions. In the following examples, in the disclosure of any measurements, including temperatures, pressures, times, weights, percents, concentrations, ranges, chemical shifts, frequencies, molar ratio, and the like, it is to be understood that such measurements are respectively, "about."

EXAMPLES

Example 1

Synthesis of (3-chloro-4-methoxyphenyl)-(2-pyridin-4-ylquinolin-4-yl) amine **(E 1)**

Step (i): *Synthesis of N-(2-acetylphenyl) isonicotinamide* **(1)**



1

To a mixture of orthoaminoacetophenone (2.0 grams, 14.8 mmol) and triethylamine (7.2 mL, 52.0 mmol) in dry tetrahydrofuran (15 mL) was added

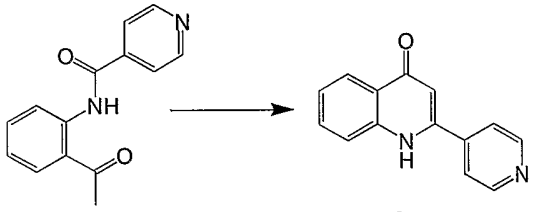
dropwise to a freshly prepared isonicotinyl chloride (2.5 grams, 17.8 mmol) dissolved in 50 mL of tetrahydrofuran, while the mixture was stirred under a nitrogen atmosphere at 0 °C. After this mixture was stirred at 0 °C for 2 hours, the reaction mixture was allowed to warm to room temperature, and stirred overnight. The resulting mixture was poured into ice-cold water and partitioned in ethyl acetate (2 x 250 mL). The organic layers were collected and washed with water (100 mL) followed by saturated sodium chloride (125 mL) solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue thus obtained was purified by column chromatography using ethyl acetate and petroleum ether, followed by washing with diethyl ether to afford the desired product (**1**) as a pink colored solid (0.975 gram); Yield: 28%.

^{1}H NMR ($CDCl_3$, 200 MHz):δ 12.89 (br s, D_2O exchangeable, NH), 8.94 (d, J = 8.4 Hz, 1H), 8.83 (d, J = 5.6 Hz, 2H), 7.99 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 5.9 Hz, 2H), 7.65 (t, J = 8.1 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 2.74 (s, 3H).

IR (KBr, cm^{-1}): 3439.7, 1675.0, 1644.4, 1522.5, 1249.0, 757.5.

MS: (CI) m/z: 241 (M^++1).

Step (ii): *Synthesis of 2-pyridin-4-yl-1H-quinolin-4-one* **(2)**



1 2

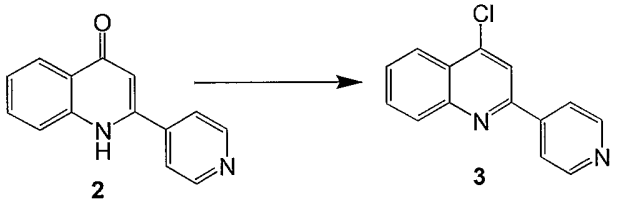
To a solution of compound **1** (0.9 grams, 3.75 mmol, prepared in step (i)) in *t*-butanol (15 mL) was added potassium-*tert*-butoxide(1.05 grams, 9.4 mmol), and the resulting mixture was heated to reflux with stirring, under a nitrogen atmosphere, for about 5 to about 6 hours. The mixture was then cooled to room temperature, evaporated to dryness and reconstituted and diluted with ice-cold water. This water mixture was then neutralized (pH about 7.0) with cold 2N hydrochloric acid, with stirring. The yellow solid that separated out was stirred, filtered off, and dried under vacuum to afford the title compound (0.680 gram); Yield: 82 %.

^{1}H NMR ($CDCl_3$, 200 MHz):δ 11.85 (s, D_2O exchangeable, -NH), 8.85 (d, J = 5.9 Hz, 2H), 8.13 (d, J = 7.8 Hz, 1H), 7.89-7.55 (m, 4H), 7.39 (t, J = 7.3 Hz, 1H), 6.51 (s, 1H).

IR (KBr, cm^{-1}): 3209.8, 1596.1, 1563.2, 1516.3.

Mass spec (CI) m/z: 223 (M^++1).

Step (iii): *Synthesis of 4-chloro-2-pyridin-4-ylquinoline* **(3)**



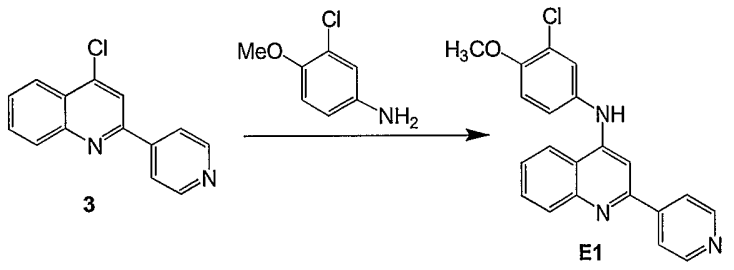
A mixture of compound **2** prepared as above (0.6 grams, 2.70 mmol) and phosphorus oxychloride (10 mL) was refluxed for 8 to 10 hours. The reaction was monitored by thin layer chromatography. After completion of the reaction, the phosphorus oxychloride was distilled off completely, and the residue was reconstituted and diluted with ice-cold water. The mixture was then neutralized (pH about 7.0) using sodium bicarbonate solution. The solid that separated our was filtered off, washed with water, and dried to afford the desired compound (0.490 gram); Yield: 76%.

^{1}H NMR (200 MHz, $CDCl_3$):δ 8.80 (d, J = 6.2 Hz, 2H), 8.24 (t, 10.10 Hz, 2H), 8.06-8.00 (m, 3H), 7.87-7.65 (m, 2H).

IR (KBr, cm^{-1}) 1584.4, 1541.1, 1488.6, 1418.6, 830.8, 757.5.

Mass spec (CI) m/z: 241 (M^++1).

Step (iv): *Synthesis of (3-chloro-4-methoxyphenyl)-(2-pyridin-4-ylquinolin-4-yl) amine* **(E 1)**



A mixture of compound **3** (0.2 grams, 0.83 mmol) and 3-chloro-*para*-anisidine (0.14 grams, 0.92 mmol) in isopropyl alcohol (5 mL) was heated to reflux for 12 hours under a nitrogen atmosphere. The solid that separated was filtered off while hot

and then washed with isopropanol (5.0 mL). The yellow solid thus obtained was dried under vacuum to give the desired compound (0.210 gram); Yield: 70%.

Melting Point:280-282 °C.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 11.10 (br s, D_2O exchangeable,-NH), 8.89-8.86 (m, 3H), 8.39 (d, J = 8.4 Hz,1H), 8.08-7.97 (m, 3H), 7.81 (t, J = 7.3 Hz, 1H), 7.66 (d, J = 2.2 Hz,1H), 7.55 (d, J = 7.7 Hz,1H), 7.32 (d, J = 8.7 Hz, 1H), 7.03 (s,1H), 3.93 (s, 3H).

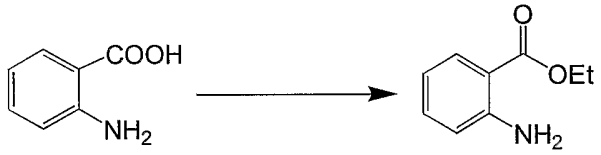
IR(KBr, cm^{-1}): 3431, 1590.5, 1550.3, 1448.8, 1258.5.

Mass spec (CI) m/z: 363 (M^++1).

Example 2

Synthesis of (3-chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine **(E 2)**

Step (i): *Synthesis of 2-amino-benzoic acid ethyl ester* **(4)**



4

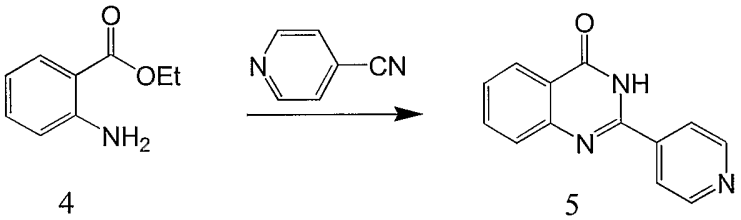
A mixture of anthranilic acid (3.0 grams, 21.89 mmol) and thionyl chloride (5.21 grams, 43.78 mmol) in ethanol (25 mL) was heated at reflux (80 °C) for 12 hours. The solvent was then removed and the residue was reconstituted and diluted with ice-cold water. The resulting mixture was then neutralized (pH about 7.0) by using sodium bicarbonate solution and extracted with ethyl acetate (3 x 30 mL). The organic layers were collected, combined, washed with water (2 x 15 mL), dried over anhydrous sodium sulfate, and concentrated to give the desired compound (2.2 grams); Yield: 61 %.

^{1}H NMR (200 MHz, DMSO-d_6): δ 7.86 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.63 (t, J = 7.8 Hz, 2H), 5.71 (br s, NH), 4.37-4.27 (m, 2H), 1.37 (t, J = 7.3 Hz, 3H).

IR (KBr, cm^{-1}): 3482, 1689.

Mass spec (CI) m/z: 166 (M^++1).

Step (ii): *Synthesis of 2-pyridine-4-yl-3H-quinazolin-4-one* **(5)**



4 5

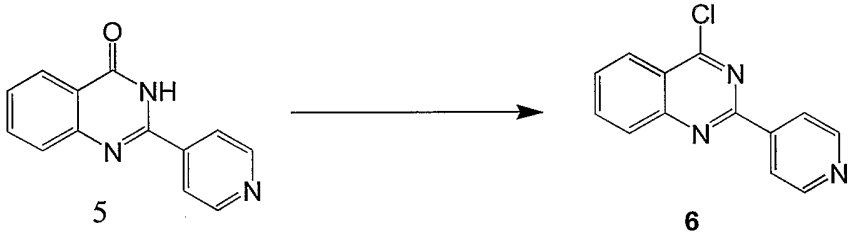
A mixture of compound **4** (2.2 grams, 13.33 mmol), 4-cyanopyridine (1.66 grams, 15.96 mmol) in 1,4-dioxane (50 mL) was stirred for 10 minutes at 25 °C. Hydrochloric acid gas was then passed through the mixture for 1 hour, and then the mixture was heated to 80 °C for 16 hours under a nitrogen atmosphere. After this time, the mixture was cooled to room temperature. The solid that separated out was filtered off and then dissolved in water. This solution was then neutralized (pH about 7.0) by using sodium bicarbonate solution. The yellow solid that separated out was filtered off, washed with water, and dried to give the desired compound (1.5 grams); Yield: 50 %.

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.77 (br s, D_2O exchangeable,-NH), 8.79 (d, J=7.9 Hz, 2H), 8.21-8.10 (m, 3H), 7.89-7.78 (m, 2H), 7.59 (t, J = 7.8 Hz, 1H).

IR (KBr, cm^{-1}): 3280, 1657.

Mass spec (CI) m/z: 224 (M^++1).

Step (iii): *Synthesis of 4-chloro-2-pyridin-4yl-quinazoline* **(6)**



5 6

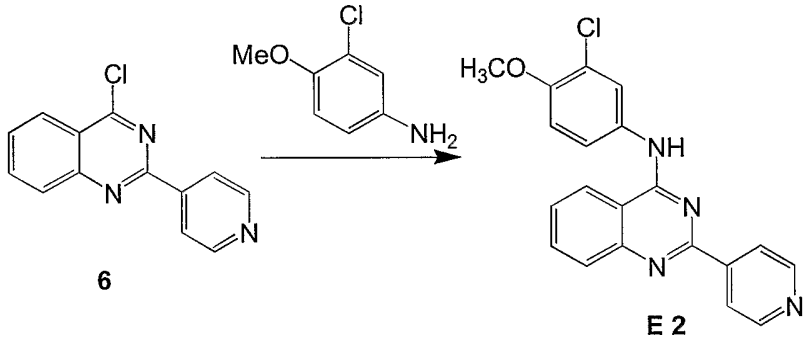
A mixture of compound **5** (1.0 grams, 4.48 mmol) in phosphorus oxychloride (20 mL) was heated to reflux for 12 hours under a nitrogen atmosphere. After this time, the phosphorus oxychloride was distilled off completely and the residue was reconstituted and diluted with ice-cold water. This mixture was then neutralized (pH about 7.0) by using sodium bicarbonate solution. The solid that separated out was filtered off, washed with water, and dried to give the desired compound (0.85 gram); Yield: 78%.

^{1}H NMR (200 MHz, DMSO-d_6) δ 8.82 (d, J = 4.7 Hz, 2H), 8.33 (d, J = 5.9 Hz, 2H), 8.20-7.95 (m, 4H).

IR (KBr, cm^{-1}): 1595.

Mass spec (CI) m/z: 242 (M^++1).

Step (iv): *Synthesis of (3-chloro-4-methoxy-phenyl)-(2-pyridin-4yl-quinazolin-4-yl)-amine* **(E 2)**



A mixture of compound **6** (0.2 grams, 0.82 mmol) and 3-chloro-*para*-anisidine (0.13 grams, 0.82 mmol) in isopropyl alcohol (10 mL) was heated and refluxed for 3 hours under a nitrogen atmosphere. The resulting solid that separated our was filtered while hot and then washed with isopropanol (2.0 mL). The yellow solid thus obtained was dried under vacuum to give the desired compound (0.270 gram); Yield: 90%.

Melting point: >220 °C.

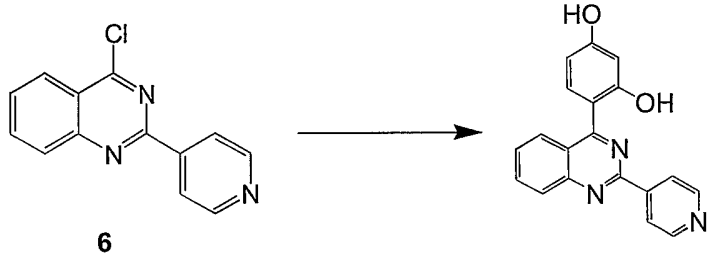
^{1}H NMR (200 MHz, DMSO-d_6) 10.95 (br s, 1H), 9.67 (s, 2H), 9.41 (d, J = 7.5 Hz, 2H), 9.24 (s, 2H), 8.87-8.49 (m, 4H), 8.00 (d, J = 9.3 Hz, 1H), 4.70 (s, 3H).

IR (KBr, cm^{-1}):3442.

Mass spec (CI) m/z: 363 (M^++1).

Example 3

Synthesis of 4-(2-pydrin-4-yl-quinazolin-4-yl)-benzene-1,3-diol **(E 3)**

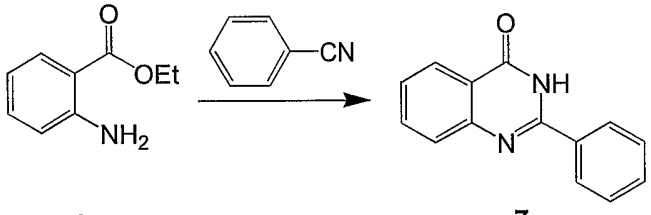


A mixture of compound **6** (0.20 grams, 0.82 mmol) and aluminum chloride ($AlCl_3$, 0.26 grams, 1.99 mmol) was prepared in dichloroethane (10 mL) and benzen-1,3-diol (0.09 grams, 0.82 mmol) was added dropwise under an anhydrous atmosphere. This mixture was stirred at 25 °C for 30 minutes and then at 80 °C for 24 hours. The resulting mixture was then cooled to room temperature, poured into water (30 mL), and extracted with chloroform (3 x 20 mL). The organic layers were collected, combined, dried over anhydrous sodium sulfate, and then concentrated. The residue thus obtained was purified by column chromatography using 20% ethyl acetate and petroleum ether to afford the desired compound (0.110 gram); Yield: 66%.
Melting point: 280-282 °C.
^{1}H NMR (200 MHz, DMSO-d_6) δ 9.90 (br s, 1H), 9.84 (br s, 1H), 8.78 (s, 2H), 8.41 (s, 2H), 8.41-7.96 (m, J = 7.1 Hz, 3H), 7.73 (t, J = 7.1 Hz, 1H), 7.36 (d, J = 9.5 Hz, 1H), 6.48 (d, J = 9.5 Hz, 2H).
IR (KBr, cm^{-1}): 3445, 2940.
Mass spec (CI) m/z: 316 (M^+, 100).

Example 4

Synthesis of 4-(2-phenyl-quinazolin-4-yl)-benzene-1,3-diol **(E 4)**

Step (i): *Synthesis of 2-phenyl-3H-quinazolin-4-one* **(7)**



4 7

A solution of compound **4** (2.2 grams, 13.33 mmol) and 4-cyanobenzene (30 mL) was stirred for 10 minutes at 25 °C. Hydrochloric gas was then passed through the mixture for 1 hour and then the mixture was heated to 80 °C for 3 hours under a nitrogen atmosphere. This mixture was cooled to room temperature and the solid that separated was filtered off, and then dissolved in water. This aqueous mixture was then neutralized (pH about 7.0) using sodium bicarbonate solution. The yellow solid

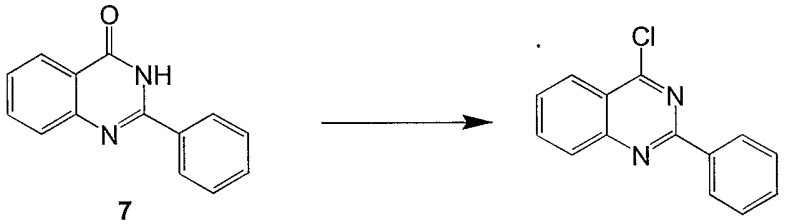
that separated was filtered off, washed with water, and dried to give the desired compound (1.9 grams); Yield: 94 %.

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.53 (br s, D_2O exchangeable,-NH), 8.20-8.14 (m, 2H), 7.88-7.72 (m, 3H), 7.58-7.49 (m, 4H).

IR (KBr, cm^{-1}):3445, 1673.

Mass spec (CI) m/z: 223 (M^++1).

Step (ii): *Synthesis of 4-chloro-2-phenyl-quinazoline* **(8)**



7 8

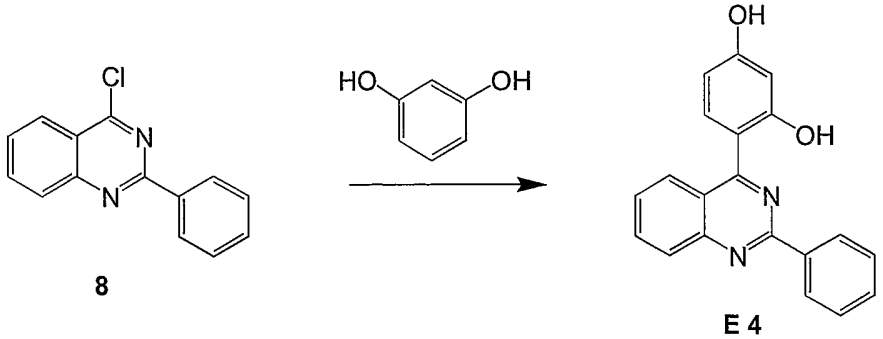
A mixture of compound **7** (2.0 grams, 9.09 mmol) in phosphorus oxychloride (20 mL) was heated and refluxed for 12 hours under a nitrogen atmosphere. After this time, the phosphorus oxychloride was distilled off completely, and the residue was reconstituted and diluted with ice-cold water. The mixture was then neutralized (pH about 7.0) using sodium bicarbonate solution. The solid that separated was filtered off, washed with water and dried to give the desired compound (1.6 grams). Yield: 73 %.

^{1}H NMR (200 MHz, DMSO-d_6): δ 8.62-8.57 (m, 2H), 8.26 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.94 (t, J = 7.3 Hz, 1H), 7.67 (t, J = 6.8 Hz, 2H), 7.63-7.51 (m, 2H).

IR (KBr, cm^{-1}): 1590.

Mass spec (CI) m/z: 241 (M^++1).

Step (iii) : *Synthesis of 4-(2-phenyl-quinazolin-4-yl)-benzen-1,3-diol* **(E 4)**



8 E 4

To a stirring mixture of **8** (0.25 grams, 0.82 mmol) and aluminum chloride ($AlCo_3$, 0.26 grams, 1.94 mmol) in dichloroethane (10 mL) was added benzen-1,3-diol (0.09 grams, 0.81 mmol) dropwise under an anhydrous atmosphere. This mixture was stirred at 25 °C for 30 minutes and then stirred at 80 °C for 24 hours. The resulting mixture was cooled to room temperature, poured into water (30 mL), and extracted with chloroform (3 X 20 mL). The organic layers were collected, combined, dried over anhydrous sodium sulfate, and then concentrated. The residue thus obtained was purified by column chromatography using 20% ethyl acetate/petroleum ether to afford the desired compound (0.150 gram); Yield: 58%.

Melting point: 178-180 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ 9.78 (br s, 1H), 8.37 (d, J = 8.1 Hz, 2H), 8.26 (t, J = 4.0 Hz, 1H), 8.04 (d, J =3.5 Hz, 2H), 7.77 (t, J = 3.5 Hz, 1H), 7.48 (d, J = 5.1 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 6.88-6.77 (m, 2H).

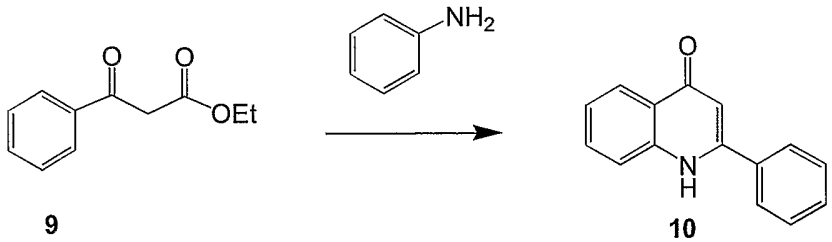
IR (KBr, cm^{-1}) : 3425.

Mass spec (CI) m/z: 315 (M^++1).

Example 5

Synthesis of (3-chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine **(E 5)**

Step (i): *Synthesis of 2-phenyl-1H-quinolin-4-one* **(10)**



9 **10**

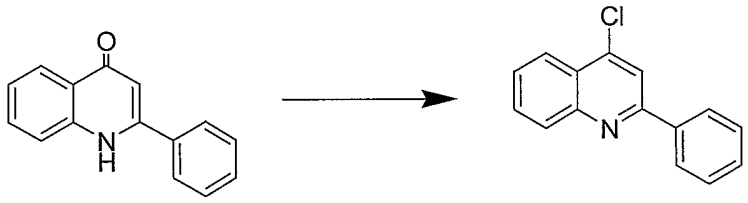
A mixture of aniline (5.0 grams, 53.7 mmol), ethyl benzoylacetate (**9**) (10.33 grams, 53.7 mmol) and polyphosphoric acid (15.0 grams) was heated to between about 90 °C to about 100 °C for 6 hours under a nitrogen atmosphere. After this time, cold water was added to the reaction mixture and this mixture was stirred for 2 hours. The solid that separated out was filtered off, washed with water and dried under vacuum to give the desired compound (4.63 gram); Yield: 39%.

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.0 (br s, D_2O exchangeable,-NH), 8.12 (d, J = 8.1 Hz, 2H), 7.88-7.58 (m, 6H), 7.36 (t, J = 8.1 Hz, 1H), 6.42 (s, 1H).

IR (KBr, cm^{-1}):1642, 1594.

Mass spec (CI) m/z: 222 (M+1).

Step (ii): *Synthesis of 4-chloro-2-phenyl-quinoline* **(11)**



10 **11**

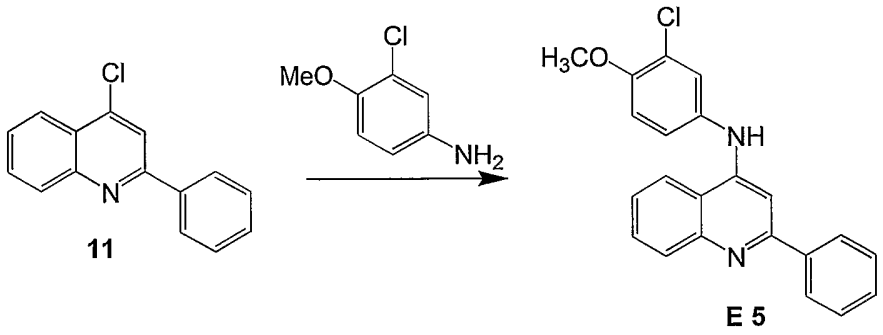
A mixture of compound **10** (1.0 grams, 4.5 mmol) in phosphorus oxychloride (20 mL) was heated to reflux for 4 hours under a nitrogen atmosphere. After this time, the phosphorus oxychloride was distilled off completely and the residue was reconstituted and diluted with ice-cold water. The mixture was then neutralized (pH~7.0) using sodium bicarbonate solution. The solid that separated was filtered off, washed with water and dried to give the desired compound (0.540 gram); Yield 50 %.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.73 (d, J = 8.3 Hz, 2H), 8.43-7.94 (m, 7H), 7.69 (s, 1H).

IR (KBr, cm^{-1}):1631, 984.

Mass spec (CI) m/z: 240 (M^++1).

Step (iii): *Synthesis of (3-chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine* **(E 5)**



11 **E 5**

A mixture of compound **11** (0.3 grams, 1.2 mmol) and 3-chloro-*para*-anisidine (0.19 grams, 1.2 mmol) in isopropyl alcohol (15 mL) was heated and refluxed for 4 hours under a nitrogen atmosphere. The solid that separated was

filtered off while hot and then washed with 5.0 mL of isopropanol. The yellow solid thus obtained was dried under vacuum to give the desired compound (0.212 gram); Yield: 47%.

Melting range: 272-274 °C.

^{1}H NMR (200 MHz, DMSO-d_6) :11.10 (s, D_2O exchangeable, 1H), 8.87 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.04 (t, J =8.0 Hz, 1H), 7.92-7.54 (m, 8H), 7.32 (d, J = 7.8 Hz, 1H), 6.89 (s, 1H), 3.93 (s, 3H, OCH_3).

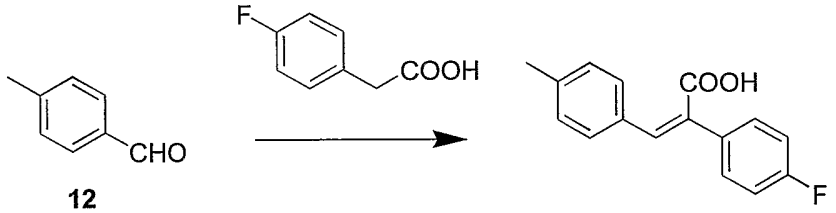
IR (KBr, cm^{-1}):1610, 1501.

Mass spec (CI) m/z: 361 (M^++1, 100%).

Example 6

Synthesis of (3-chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine **(E 6)**

Step (i): *Synthesis of 3-(4-methylphenyl)-2-(4-fluoro phenyl)-2-propenoic acid* **(13)**



12 **13**

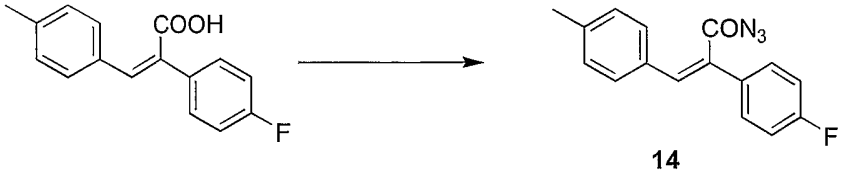
A mixture of compound **12** (15 grams, 125 mmol) and 4-fluoro phenyl acetic acid (19.24 grams, 125mmol), acetic anhydride (25 mL), and triethylamine (12.9 mL, 93.75 mmol) was refluxed for about 5 to about 6 hours under a nitrogen atmosphere, after which time the remaining acetic anhydride was distilled off at the same temperature. The residue was reconstituted and diluted with water (100 mL) and neutralized with 2N hydrochloric acid. The solid that precipitated was filtered off and dried under vacuum to afford the title compound (17 grams) as a pale brown solid. Yield: 53%.

^{1}H NMR: (DMSO-d_6, 200 MHz): 7.93 (s, H), 7.25-6.93 (m, 8H), 2.29 (s, 3H).

IR (KBr, cm^{-1}): 1673.

Mass spec (CI) m/z: 257 (M^++1).

Step (ii): *Synthesis of 3-(4-methylphenyl)-2-(4-fluoro phenyl)-2-propionic azide* **(14)**



13 14

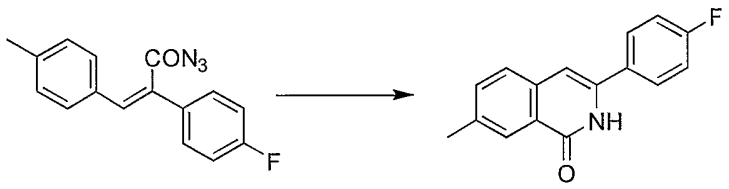
To a cooled (0 °C) mixture of compound **13** (17 grams, 66.4 mmol) and triethylamine (7.3 grams, 73 mmol) in acetone (150 mL) was added a solution of ethylchloroformate (9.73 grams, 89.6 mmol) in acetone (60 mL) dropwise followed by the addition of a sodium azide solution (6.26 grams, 99.6 mmol, in 20 mL water). The resulting reaction mixture was stirred at room temperature for 1 h, poured into ice water (800 mL), and then filtered. The solid that separated was filtered off, washed with excess water, dried for 15 hours to afford the title compound (15 grams) as a yellow solid. Yield: 80%.

^{1}H NMR: (DMSO-d_6, 200 MHz): 7.88 (s, H), 7.31-6.84 (m, 8H), 2.27 (s, 3H).

IR: (KBr, cm^{-1}): 1664.

Mass spec (CI) m/z: 281 (M^++1).

Step (iii): *Synthesis of 3-(4-fluoro Phenyl) -7-methyl -1,2-dihydro-1-isoquinoline* **(15)**



14 15

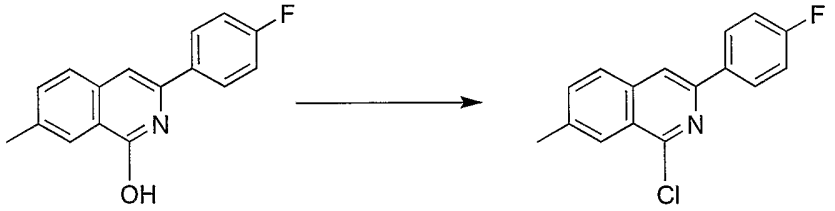
A mixture of compound **14** (15 grams, 53.3 mmol) and tributylamine (10.5 mL) in diphenylether (150 mL) was stirred at 250 °C for 30 minutes under a nitrogen atmosphere. After this time, the diphenylether was distilled off at the same temperature. The residue was cooled, treated with toluene (500 mL), and the product was re-crystallized from ethyl acetate to afford the title compound (12 grams); Yield: 89%.

^{1}H NMR (DMSO-d_6, 200 MHz): 11.47 (s, NH), 8.02 (s, H), 7.86-6.9 (m, 6H), 6.8 (s, H), 2.45 (s, 3H).

IR (KBr, cm^{-1}): 2921, 1637,

Mass spec (CI) m/z: 254 (M^++1).

Step (iv): *Synthesis of 1-Chloro- 3-(4-fluoro Phenyl) -7-methyl -1H- isoquinoline* **(16)**



15 **16**

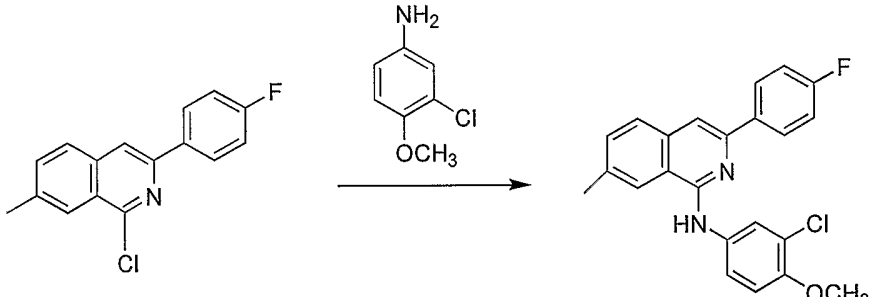
A mixture of compound **15** (8.0 grams, 31.7 mmol) and phosphorus oxychloride (50 mL) was stirred at refluxing temperature for 8 hours. After this time, the remaining phosphorus oxychloride was distilled off at the same temperature. The residue was reconstituted and diluted with water and neutralized with a sodium bicarbonate solution. The solid that formed was dried under vacuum to afford the title compound (5.48 grams); Yield: 64%.

^{1}H NMR: ($CDCl_3$, 200 MHz): 8.1-8.03 (m, 2H), 7.8 (s, H), 7.74 (d, J = 8.4 Hz, H), 7.55 (d, J = 8.4 Hz, H), 7.19-7.11 (m, 2H), 6.8 (S, 1H), 2.57 (s, 3H).

IR: (KBr, cm^{-1}): 1600.

Mass spec (CI) m/z: 272 (M^++1, 100%).

Step (v): *Synthesis of (3-chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine* **(E 6)**



16 **E 6**

A mixture of compound **16** (0.3 grams, 1.1mmol) and 3-chloro-4-methoxyaniline (0.17 grams, 1.1mmol) in butanol (10 mL) was allowed to stir at refluxing temperature for 36 hours under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature. The solid that precipitated was filtered off and dried under vacuum to afford the title compound (0.3 grams) as an off-white solid. Yield: 69%.

Melting Range: 154-156 °C.

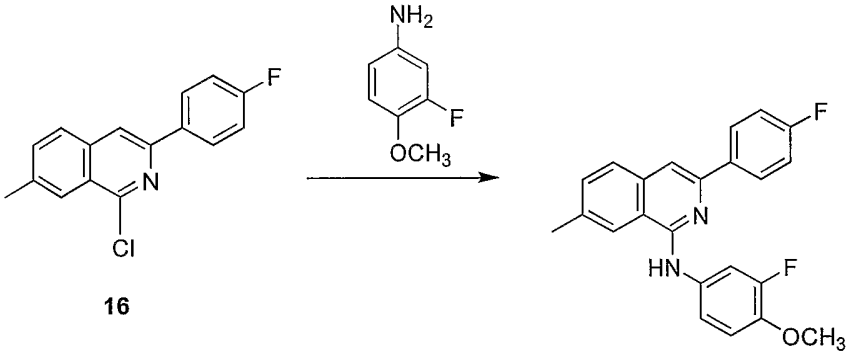
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11-8.02 (m, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.60-7.56 (m, 2H), 7.5 (s, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.04 (br s, 1H), 6.99-6.95 (m, 2H), 3.93 (s, 3H), 2.56 (s, 3H).

IR: (KBr, cm^{-1}): 3435.

Mass spec (CI) m/z: 392 (M^++1, 100%).

Example7

Synthesis of (3-fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine **(E 7)**



A mixture of compound **16** (0.3 grams, 1.1 mmol) and 3-fluoro-4-methoxyaniline (0.19 grams, 1.1 mmol) in butanol (10 mL) was allowed to stir at refluxing temperature for 36 hours under a nitrogen atmosphere. After this time, the reaction mixture was cooled to room temperature. The solid that precipitated was filtered off and dried under vacuum to afford the title compound. Yield:57%.

Melting Range: 163-165 °C.

^{1}H NMR (200 MHz, DMSO-d_6) :δ8.09-8.02 (m, 2H), 7.74 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.52-7.48 (m, 2H), 7.33-6.90 (m, 4H), 3.92 (s, 3H), 2.5 (s, 3H).

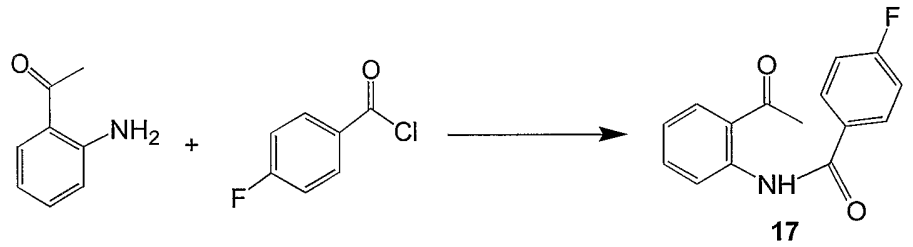
IR: (KBr, cm^{-1}): 3416

Mass spec (CI) m/z: 377 (M^++1, 100%).

Example 8

Synthesis of (3-chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine **(E 8)**

Step (i): *Synthesis of N-(2-acetyl-phenyl)-4-fluoro-benzamide* **(17)**



17

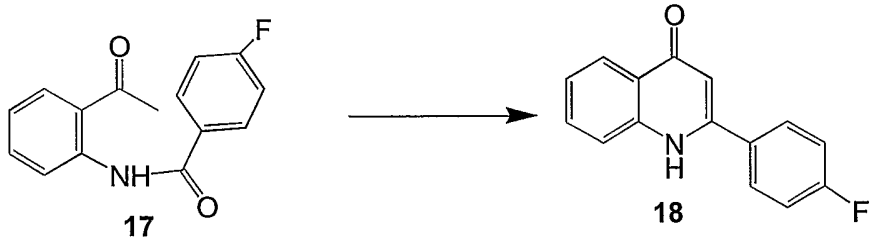
To a solution of 2-aminoacetophenone (10 grams, 74.07 mmol) in dichloromethane (75 mL) was added triethylamine (15.5 mL, 111.10 mmol) at 25 °C under a nitrogen atmosphere. The mixture was then stirred at 0 °C for 30 minutes. To this mixture was added a freshly prepared 4-fluorobenzoyl chloride (15.21grams, 96.3 mmol) slowly. The mixture was stirred at 25 °C for 12 hours. The mixture was concentrated and diluted with water. The solid precipitated was filtered, dried under vacuum to afford the title compound 14 grams. Yield: 74%.

^{1}H NMR (DMSO-d_6): δ 12.69 (br s, D_2O exchangeable,-NH), 8.94 (d, J = 8.5 Hz,1H), 8.12-7.94 (m, 3H), 7.63 (t, J = 7.3 Hz, 1H), 7.24-7.14 (m, 3H), 2.73 (s, 3H).

IR (KBr, cm^{-1}):1639, 1588, 1540, 1446.

Mass spec (CI) m/z: 258 (M^++1, 100%).

Step (ii): *Synthesis of 2-(4-fluoro-phenyl)-1H-quinolin-4-one* **(18)**



17 18

To a solution of compound **17** (14 grams, 54.5 mmol) in *t*-butanol (125 mL) was added potassium-*tert*-butoxide (18.3 grams, 163.4 mmol) at 25 °C under a nitrogen atmosphere. The mixture was then stirred at refluxing temperature for 12 hours. The mixture was then cooled to room temperature, concentrated under vacuum and diluted with cold 2N hydrochloric acid until the pH was about 7. The solid that

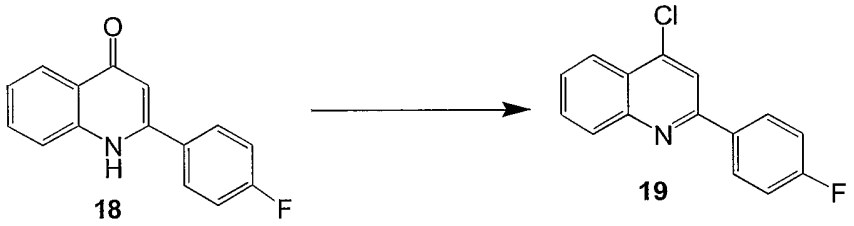
precipitated was filtered off, dried, treated with ethyl acetate, and then filtered to afford the title compound 8.5 grams. Yield: 65 %.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (br s, D_2O exchangeable,-NH), 8.08 (d, J = 8.1 Hz,1H), 7.92-7.88 (m, 2H), 7.76-7.67 (m, 2H), 7.46-7.41 (m, 2H), 7.36-7.32 (m, 1H), 6.32 (s, 1H).

IR (KBr, cm^{-1}): 3426, 1547, 1507.

Mass spec (CI) m/z: 240 (M^++1).

Step (iii): *Synthesis of 4-chloro-2-(4-fluoro-phenyl)-quinoline* **(19)**



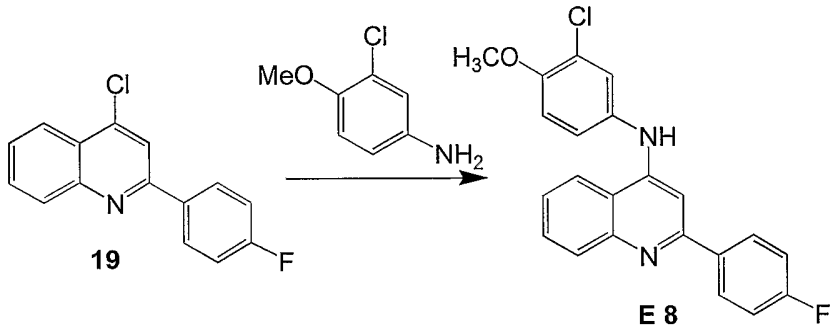
A mixture of compound **18** (8.5 grams, 35.5 mmol) and phosphorus oxychloride (100 mL) was stirred at refluxing temperature for about 12 hours. The remaining phosphorus oxychloride was distilled off at the same temperature. The residue was reconstituted and diluted with water and then neutralized with sodium bicarbonate solution until the pH was about 7.0. The mixture was extracted with ethyl acetate (3 X 50 mL). The organic layers collected, combined, washed with water (2 x 50 mL), dried over anhydrous sodium sulfate, and concentrated. The residue thus obtained was purified by column chromatography using 20% ethyl acetate / petroleum ether to afford the desired compound (7.5 grams). Yield: 82%.

^{1}H NMR (DMSO-d_6) δ 8.24-8.21 (m, 1H), 8.17-8.13 (m, 3H), 7.93 (s, 1H), 7.80-7.76 (m, 1H), 7.64-7.60 (m, 1H), 7.23-7.19 (m, 2H).

IR (KBr, cm^{-1}):1583, 1493, 838.

Mass spec (CI) m/z: 258 (M^++1).

Step (iv): *Synthesis of (3-chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine* **(E 8)**



A mixture of compound **19** (5.5 grams, 21.4 mmol) and 3-chloro-4-methoxybenzene (3.70 grams, 23.5 mmol) in isopropanol (50 mL) was allowed to stir at refluxing temperature for 12 hours under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature. The solid that precipitated was filtered off and dried under vacuum to afford the title compound (5.0 grams) as a yellow solid. Yield: 62%.

Melting point: 260 °C.

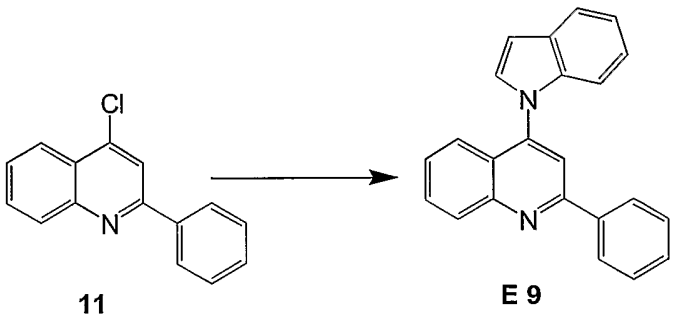
^{1}H NMR (200 MHz, DMSO-d_6) : δ11.09 (s, D_2O exchangeable, 1H), 8.81 (d, J = 8.1 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.3 Hz, 1H), 8.02-7.45 (m, 7H), 7.32 (d, J = 8.7 Hz, 1H), 6.88 (s, 1H), 3.93 (s, 3H).

IR (KBr, cm^{-1}): 1608, 1589.

Mass spec (CI) m/z: 379 (M^++1).

Example 9

Synthesis of 4-indol-1-yl-2-phenyl-quinoline **(E 9)**



To a cooled (0 °C) suspension of 60% sodium hydride (75 mg, 1.9 mmol) in dimethylformamide (DMF) (3 mL) was added a solution of indole (0.15 grams, 1.3

mmol) in dimethylformamide (DMF) (2 mL), with stirring, under a nitrogen atmosphere. This mixture was stirred for 30 minutes, after which time a solution of compound **11** (0.3 grams, 1.3 mmol) in dimethylformamide (DMF) (3 mL) was added at the same temperature. The mixture was then heated to 80 °C for 5 hours, after which time the mixture was cooled to room temperature and then poured into ice cold water. The solid that precipitated was filtered off, dried under vacuum, and then purified by column chromatography using 4% ethyl acetate and petroleum ether to afford the title compound (0.201 gram). Yield: 50%.

Melting range: 100-102 °C.

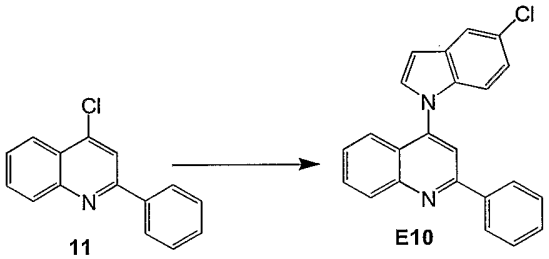
^{1}H NMR (200 MHz, $CDCl_3$): 8.30 (d, J = 8.6 Hz, 1H), 8.20-8.17 (m, 2H), 7.96 (s, 1H), 7.81-7.72 (m, 3H), 7.56-7.45 (m, 4H), 7.27-7.18 (m, 4H), 6.85-6.84 (s, 1H).

IR (KBr, cm^{-1}): 3746, 3420, 3051.

Mass spec (CI) m/z: 321 (M^++1).

Example 10

Synthesis of 4-(5-chloro-1H-indol-1-yl)-2-phenyl-quinoline **(E 10)**



11 E10

To a cooled (0 °C) suspension of 60% sodium hydride (0.075 grams, 1.9 mmol) in dimethylformamide (DMF) (3 mL) was added a solution of 5-chloroindole (0.19 grams, 1.3 mmol) in dimethylformamide (DMF) (2 mL), with stirring, under a nitrogen atmosphere. This mixture was stirred for 30 minutes, after which time a solution of compound **11** (0.3 grams, 1.3 mmol) in dimethylformamide (DMF) (3 mL) was added at the same temperature. The mixture was then heated to 80 °C for 5 hours, allowed to cool to room temperature, and then poured into ice-cold water. The solid that precipitated was filtered off, dried under vacuum, and then purified by column chromatography using 4% ethyl acetate and petroleum ether to afford the title compound (0.290 gram). Yield: 66 %.

Melting range: 148-150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 8.30 (d, J = 8.3 Hz, 1H), 8.19 (d, J = 1.6 Hz, 2H), 7.93 (s, 1H), 7.82-7.80 (m, 1H), 7.78-7.77 (m, 1H), 7.73-7.72 (m, 1H), 7.66-7.46 (m, 5H), 7.17-7.12 (m, 2H), 6.79 (s, 1H).

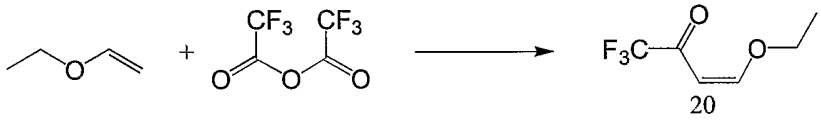
IR (KBr, cm^{-1}): 3441, 1598.

Mass spec (CI) m/z: 355 (M+1).

Examples 11 and 12

Synthesis of 2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline **(E 11)** *and 4-(3-Trifluoromethyl-pyrazol-1-yl)-2-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-quinoline* **(E 12)**

Step (i): *Synthesis of 4-(ethoxy)-1,1,1-trifluoro-3-buten-2-one* **(20)**

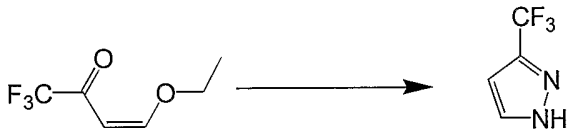


20

To a stirred solution of 4-dimethyl amino pyridine (25 mg, 0.21mmol) and trifluoroacetic anhydride (6.54 grams, 4.4 mL, 31.10 mmol) in dichloromethane (40 mL) was added ethyl vinyl ether (2.12 g, 29.4 mmol) dropwise at -10 °C. The reaction mixture was stirred for 16 hrs at 0 °C and then allowed to reach room temperature. The mixture was poured into cold sodium bicarbonate solution and the deep violet color of the reaction mixture was observed to turn yellow-brown in color. The dichloromethane layer was collected, washed with water followed by saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to dryness to give the desired compound (4-(ethoxy)-1,1,1-trifluoro-3-buten-2-one) as a brown liquid (3.3 grams, 67% yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.88 (d, *J* = 12.3 Hz, 1H), 5.86 (d, J = 12.4 Hz, 1H), 4.16-4.05 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H); m/z (CI method) 169 (M+1, 100%); IR (Neat, cm^{-1}) 1707.9, 1595.2, 724.7.

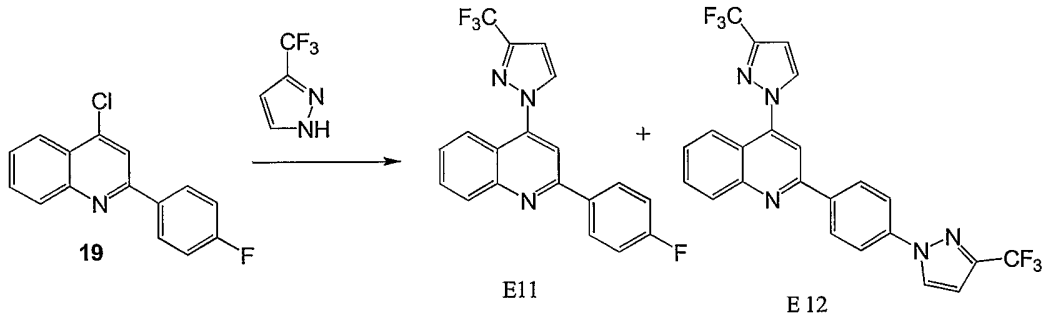
Step (ii): *Synthesis of 3-trifluoromethyl-1H-Pyrazole* **(21)**



20 21

To a stirred solution of hydrazine dihydrochloride (1 gram, 9.6 mmol) in absolute ethanol (30 mL) was added a solution of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one **(20)** (1.62 gram, 6 mmol) in ethanol (20 mL) dropwise under a nitrogen atmosphere. The mixture was refluxed for 6 hrs and then evaporated to dryness. The residue was treated with cold water (10 mL) followed by ethylacetate. The organic layer was collected, washed with water followed by saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under vacuum to give 3-trifluoromethyl-1*H*-Pyrazole as a low melting solid **(21)** (1.15 gm, 88% yield); ^{1}H NMR ($CDCl_3$) δ 12.5 (br s, D_2O exchange, NH), 7.69 (d, J = 1.4 Hz, 1H); 6.65 (d, J = 2.4 Hz, 1H); m/z (CI, method) 137 (M+1, 100%); IR (KBr, cm^{-1}) 3192.3, 2970.7, 1504.1, 1380.8, 1321.6, 776.8.

Step (iii): *Synthesis of 2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline* **(E 11) and** *4-(3-Trifluoromethyl-pyrazol-1-yl)-2-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-quinoline* **(E 12)**



19 E11 E 12

To a stirred solution of compound **21** (10.48 g, 77.04mmol) in dry DMF (250 mL) was added dry potassium carbonate (48.32 g, 350.15 mmol) at room temperature under nitrogen. After 30 minutes compound **19** (18 g, 70.03 mmol) was added to the reaction mixture and stirring continued at 80 °C for 42 hrs. The mixture was cooled to room temperature, poured into ice-cold water and extracted with ethyl acetate. The organic layer was collected, washed with water followed by saturated sodium chloride

solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography using about 1.50% to about 2.0% EtOAc / petroleum ether as eluant to afford compounds **E 11** (15.84 g, yield 75%) and **E 12** (2.88 g, yield 9%).

Compound **E 11**:

Melting range: 102-104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 8.27-8.19 (m, 3H), 8.02-7.98 (m, 2H), 7.94 (s, 1H), 7.84-7.80 (m, 1H), 7.64-7.59 (m, 1H), 7.25-7.21 (m, 2H), 6.89 (d, J = 2.4 Hz, 1H).

IR (KBr, cm^{-1}): 1601, 1502.

Mass spec (CI) m/z: 358 (M^++1).

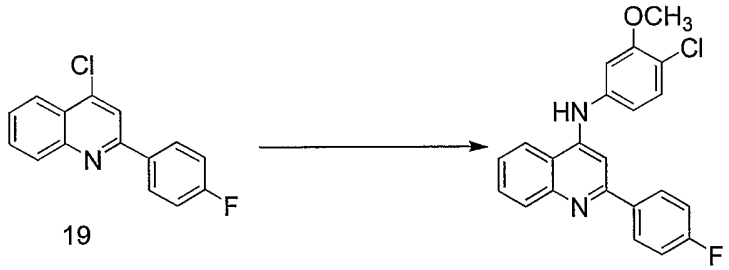
Compound **E 12**:

Melting range: 142-144 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.33 (m, 2H), 8.28 (d, J=8.4Hz, 1H), 8.05-8.00 (m, 4H), 7.91-7.82 (m, 3H), 7.65-7.61 (m, 1H), 6.90 (d, J=2.3Hz, 1H), 6.77 (d, J=2.5Hz, 1H).

Example 13

Synthesis of (4-Chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine **(E 13)**



19 E 13

A mixture of compound **19** (1.1 mmol) and 4-chloro-3-methoxyaniline (0.17 g, 1.1 mmol) in *i*-PrOH (10 mL) was stirred at refluxing temperature for 36 h under a nitrogen atmosphere. After this time, the reaction mixture was allowed to cool to room temperature. The solid that precipitated was filtered off and dried under vacuum to afford the title compound.

Melting range: 274-276 °C

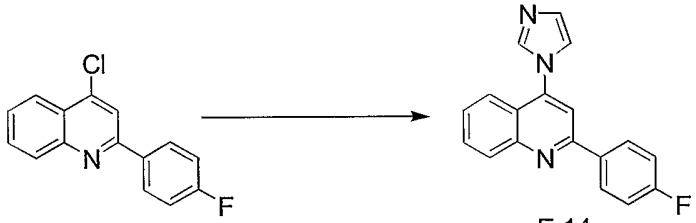
^{1}H NMR (200 MHz, DMSO-d_6) 10.89 (s, D_2O exchangeable, 1H), 8.74 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.08-7.85 (m, 3H), 7.81 (d,J=7.5Hz, 1H), 7.61-7.59 (m, 2H), 7.50 (d,J=8.9Hz, 1H), 7.36-7.35 (m,1H),7.19-7.16 (m,1H),7.09 (s,1H).3.90 (s, 3H).

IR (cm^{-1}): 1607, 1585, 1550.

MS (m/z): 379 (M^+, 100%)

Example 14

Synthesis of 2-(4-Fluoro-phenyl)-4-imidazol-1-yl-quinoline **(E 14)**



19 E 14

Imidazole (95 mg, 1.40 mmol) was added to a stirred solution of sodium hydride (75 g, 1.80 mmol) in dry DMF (5 mL) under a nitrogen atmosphere, at room temperature. After stirring this mixture for about 30 minutes, compound **19** (300 mg, 1.17 mmol) was added and the resulting reaction mixture was stirred at 80 °C for about 24 hrs. After this time, the reaction mixture was cooled to room temperature, poured into ice-cold water, and stirred. The solid that separated out was collected by filtration, stirred in hexane for 4 hrs, filtered off, and dried to give the desired product (135 mg, 40%).

Melting range:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.25 (m, 1H), 8.22-8.17 (m, 2H), 7.91 (s, 1H), 7.85-7.78 (m, 3H), 7.61-7.57 (m, 1H), 7.38-7.37 (m, 2H), 7.25-7.20 (m, 2H).

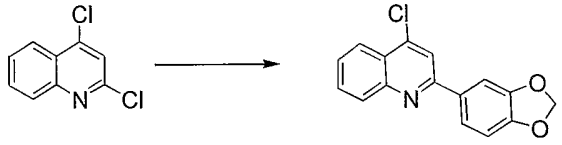
IR (cm^{-1}): 1601, 1503, 1425.

MS (m/z): 290 (M^+, 100%)

Example 15

Synthesis of 2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline **(E 15)**

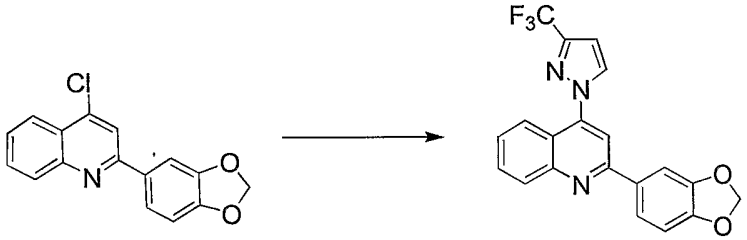
Step (i): *Synthesis of 2-Benzo[1,3]dioxol-5-yl-4-chloro-quinoline* **(22)**



22

To a stirred solution of 2,4-dichloroquinoline (300 mg, 1.52 mmol) in DMF (5 mL) was added tetrakis(triphenylphosphine)palladium (88 mg, 0.07 mmol), benzodioxale boronic acid (303 mg, 1.83 mmol), and a solution of Na_2CO_3 (1.29 g, 12.16 mmol dissolved in 6 mL of water under nitrogen. This mixture was heated to about 100 °C for about 1 hr, allowed to cool to room temperature, poured into ice-cold water, and then stirred for about 1 hr. The resulting solid that separated was filtered off, washed with water, and dried to give the desired compound.

Step (ii): *Synthesis of 2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline* **(E 15)**



22 E 15

Compound **22** (56 mg, 1.41 mmol) was added to a stirred solution of compound **21** (115 mg, 0.85 mmol) and NaH (0.85 mmol) in DMF (5.0 mL) under nitrogen. This mixture was the heated and stirred at about 80 °C to about 100 °C for 24 h, cooled to room temperature, diluted with ethyl acetate, and washed with 2N HCl. The organic layer was then collected, washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography to give the desired product (140 mg, yield 52 %).

Melting range: 98-100 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J=8.3Hz, 1H), 8.00 (d, J=1.6Hz, 1H), 7.96 (d, J=8.3Hz, 1H), 7.89 (s, 1H), 7.82-7.70 (m, 2H), 7.69-7.60 (m, 1H), 7.59-7.56 (m, 1H), 6.95 (d, J=8.3Hz, 1H), 6.88 (d, J=2.4Hz, 1H), 6.06 (s, 2H).

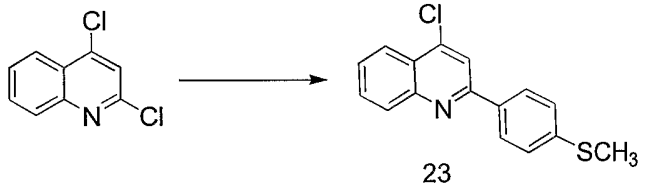
IR (cm^{-1}): 1605, 1552, 1510.

MS (m/z): 384 (M^+, 100%)

Example 16

Synthesis of 2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline (E 16)

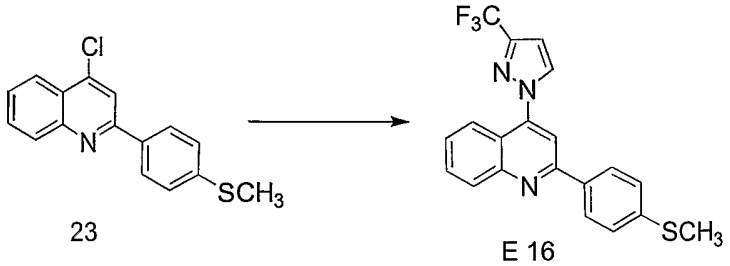
Step (i): *Synthesis of 4-Chloro-2-(4-methylsulfanyl-phenyl)-quinoline* **(23)**



23

To a stirred solution of 2,4-dichloroquinoline (300 mg, 1.52 mmol) in DMF (5.0 mL) was added tetrakis(triphenylphosphine)palladium (88 mg, 0.07 mmol), 4-methylsulfanylphenyl boronic acid (312 mg, 1.83 mmol) and a solution of Na_2CO_3 (1.29 g, 12.16 mmol dissolved in 6.0 mL of water) under nitrogen. This reaction mixture was heated to 100 °C for about 1 h, cooled to room temperature, poured into ice-cold water and then stirred for about 1.0 h, and then extracted with ethyl acetate. The organic layers were collected, combined, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography to give the desired compound; yield 89%.

Step 2: *Synthesis of 2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline* **(E 16)**



23 E 16

Compound **23** (250 mg, 0.88 mmol) was added to a stirred solution of compound **21** (136 mg, 1.75 mmol) and NaH (0.88 mmol) in DMF (5.0 mL) under nitrogen. This reaction mixture was the heated to about 80-100 °C and stirred for 24 h. After this time, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with 2N HCl. The organic layer was collected, washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulfate, and then evaporated to dryness. The residue was purified by column chromatography to give the desired product (140 mg, yield 52 %).

Melting range: 116-118 °C

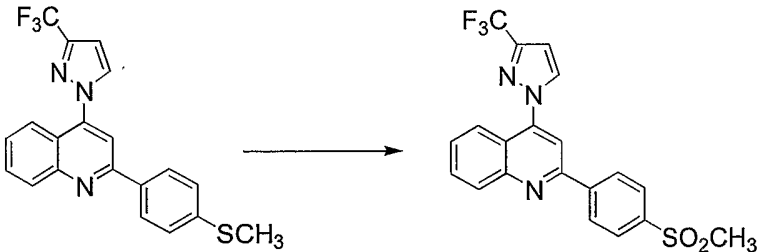
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 1H), 8.16-8.13 (m, 2H), 8.01-7.94 (m, 3H), 7.82-7.78 (m, 1H), 7.61-7.57 (m, 1H), 7.41-7.37 (m, 2H), 6.89 (d, J=2.4Hz, 1H), 2.56 (s, 3H).

IR (cm^{-1}): 1601, 1505, 1420.

MS (m/z): 385 (M^+, 100%)

Example 17

Synthesis of 2-(4-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline



E 16 E 17

Oxone (959 mg, 1.56mmol) was added to a stirred solution of compound **E 16** (200 mg, 0.52 mmol) in acetone (4 mL) and water (2 mL), at room temperature, under nitrogen. This reaction mixture was stirred for 4 hrs, poured into ice-cold water, neutralized with sodium bicarbonate solution, and extracted with EtOAc. The organic layers were collected, combined, washed with water followed by brine solution, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography to afford the desired compound (150 mg, 69%).

Melting range: 194-196 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.41 (m, 2H), 8.31 (d, J=8.3Hz, 1H), 8.14-8.11 (m, 2H), 8.06-8.03 (m, 3H), 7.89-7.85 (m, 1H), 7.70-7.66 (m, 1H), 6.91 (d, J=2.7Hz, 1H), 3.12 (s, 3H).

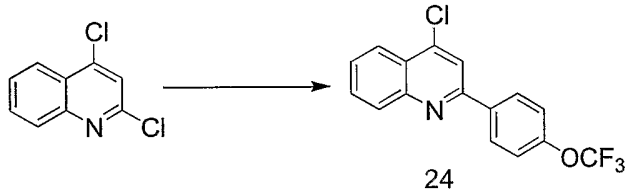
IR (cm^{-1}): 1602, 1550, 1510

MS (m/z): 418 (M^+, 100%)

Example 18

Synthesis of 2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline **(E 18)**

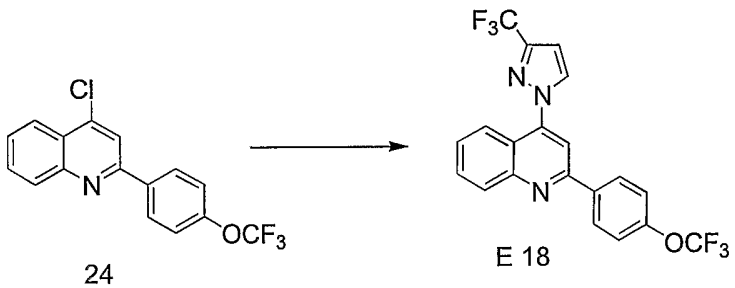
Step (i): *Synthesis of 4-Chloro-2-(4-trifluoromethoxy-phenyl)-quinoline* **(24)**



24

Tetrakis(triphenylphosphine)palladium (88 mg, 0.07 mmol) and 4-triflouromethoxy phenyl boronic acid (303 mg, 1.83 mmol) were added to a stirred solution of 2,4-dichloroquinoline (300 mg, 1.52 mmol) in DMF (5 mL), under nitrogen, followed by Na_2CO_3 (1.29 g, 12.16 mmol) dissolved in water (6 mL). The resulting mixture was then heated at 100 °C for 3 hr, cooled to room temperature, poured into ice-cold water, and stirred for about 1 hr. The solid that separated was filtered off, washed with water and dried to give the desired product.

Step (ii): *Synthesis of 2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline* **(E 18)**



24 E 18

Compound **24** (200 mg, 0.62 mmol) was added to a stirred solution of compound **21** (210 mg, 1.55 mmol) and NaH (1.55 mmol) in dry DMF (5.0 mL),

under nitrogen. The mixture was stirred at 80-100 °C for about 14 hrs. After this time, the reaction the mixture was cooled to room temperature, diluted with ethyl acetate, and washed with 2N HCl. The organic layer was collected, washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography to give the desired product (yield 55 %).

Melting range: 108-110 °C

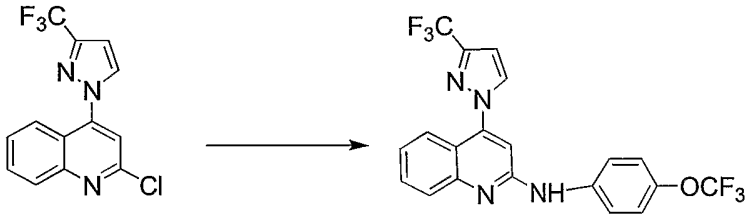
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.23 (m, 3H), 8.02-8.00 (m, 2H), 7.95 (s, 1H), 7.86-7.81 (m, 1H), 7.65-7.61 (m, 1H), 7.39-7.37 (m, 2H), 6.89 (d, J=2.7Hz, 1H).

IR (cm^{-1}): 1607, 1505, 1480

MS (m/z): 424 (M^+, 100%)

Example 19

Synthesis of (4-Trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine **(E 19)**



E 19

4-Trifluoromethoxy aniline (59 mg, 0.045 mL, 0.33 mmol) was added to a stirred solution of 2-chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline (100 mg, 0.34 mmol) in *i*-PrOH (3 mL), under nitrogen, at room temperature. This mixture was refluxed for 36 hrs and then concentrated under vacuum. The residue was dissolved in chloroform and washed with 2N HCl followed by sodium bicarbonate solution. The organic layer was collected, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography using 12-20% EtOAc / petroleum ether to give the desired compound (59 mg, 40%).

Melting range: 128-130 °C

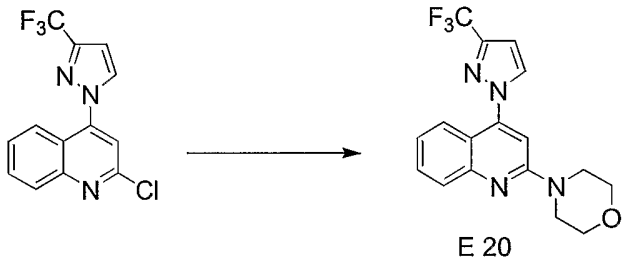
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.93 (m, 1H), 7.91-7.88 (m, 1H), 7.79-7.70 (m, 1H), 7.69-7.66 (m, 3H), 7.40-7.36 (m, 1H), 7.25-7.23 (m, 3H), 7.04 (s, 1H), 6.84 (d, J=2.4Hz, 1H).

IR (cm^{-1}): 1605, 1507, 1392

MS (m/z): 439 (M^+, 100%)

Example 20

Synthesis of 2-Morpholin-4-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline **(E 20)**



E 20

Morpholine (177 mg, 2.03 mmol) was added to a stirred solution of 2-chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline (100 mg , 0.34 mmol) in *i*-PrOH (3 mL), under nitrogen and the mixture was refluxed for 36 hrs. The resulting mixture was concentrated under vacuum, diluted with EtOAc (10 mL) and washed with 2N HCl. The organic layer was collected, washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography to give the desired product (35 mg, 30%).

Melting range: 118-120 °C

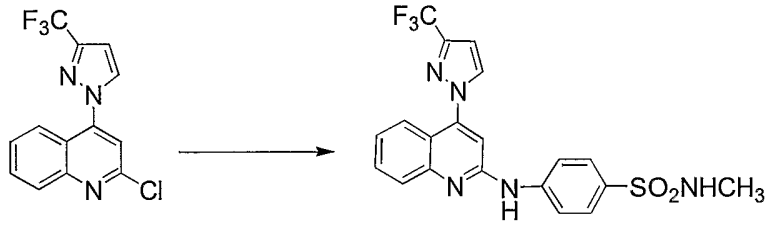
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J=2.4Hz, 1H), 7.80 (d, J=8.3Hz, 1H), 7.67-7.60 (m, 2H), 7.32-7.27 (m, 1H), 7.07 (s, 1H), 6.83 (d, J=2.4Hz, 1H), 3.87-3.84 (m, 4H), 3.77-3.75 (m, 4H).

IR (cm^{-1}): 1607, 1508, 1475.

MS (m/z): 349 (M^+, 100%)

Example 21

Synthesis of N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide **(E 21)**



E 21

4-(*N*-Methylphenyl sulphonyl) aniline (205 mg, 1.11 mmol) was added to a stirred solution of 2-chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline (300 mg, 1.01 mmol) in 1-butanol (10 mL), under nitrogen, at room temperature. This mixture was stirred under reflux for about 48 hrs and then filtered while hot. The resulting pale brown solid was stirred in *i*-PrOH, filtered off, and dried to give the desired product (225 mg, 50%).

Melting range: 220-222 °C

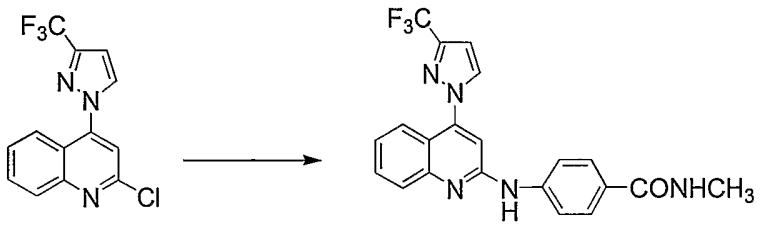
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (br s, D_2O exchange, NH), 8.14-8.11 (m, 2H), 8.03 (d, J=1.6Hz, 1H), 7.96 (d, J=8.1Hz, 1H), 7.85-7.79 (m, 3H), 7.72-7.67 (m, 1H), 7.42-7.29 (m, 2H), 6.86 (d, J=2.4Hz, 1H), 5.73 (br s, D_2Oexc, NH), 2.61 (d, J=5.1Hz, 3H).

IR (cm^{-1}): 1605, 1505, 1480

MS (m/z): 448 (M^+, 100%)

Example 22

Synthesis of N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide **(E 22)**



E 22

4-Amino-N-methyl-benzamide (166 mg, 1.11 mmol) was added to a stirred solution of 2-chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline (300 mg, 1.00 mmol) in 1-butanol (10 mL), under nitrogen, at room temperature. This reaction mixture was stirred under reflux for about 4 days and filtered while hot. The resulting pale brown solid was stirred in *i*-PrOH, filtered off, and dried to give the desired product (120 mg, 30%).

Melting range: 250-252 °C

^{1}H NMR (400 MHz, DMSO) δ 10.02 (-NH, D_2O exchangeable, 1H), 8.28-8.27 (d, J=4.50 Hz, 1H), 8.06 (d, J=8.59 Hz, 2H), 7.91-7.41 (m, 6H), 7.32 (s, 1H), 7.19-7.18 (d, J=2.41 Hz, 1H), 2.79 (s, 3H).

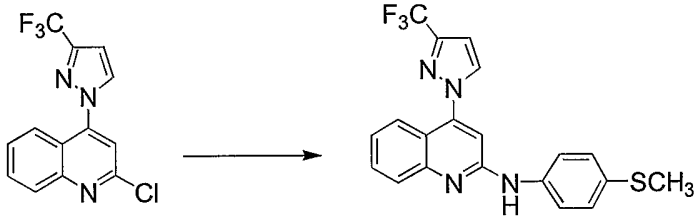
IR (cm^{-1}): 3203, 2690, 1667, 1608

MS (m/z): 412 (M^+, 100%)

Example 23

Synthesis of (4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine **(E 23)**

Step (i): *Synthesis of (4-Methylsulfanyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine*



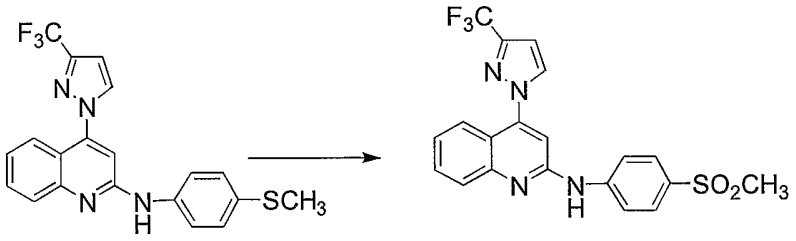
A 0.146 mL (1.2 mmol) sample of 4-thiomethyl aniline was added to a stirred solution of 2-chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline (350 mg, 1.2 mmol) in 6 mL of *i*-PrOH at room temperature, under a nitrogen atmosphere. This reaction mixture was refluxed for about 12 hrs, after which time the reaction mixture was filtered while hot, and the resulting yellow product was washed with diethyl ether and dried (yield 150 mg, 45%).

1H NMR (CDCl3, 400 MHz) 7.91-7.90 (m, 1H), 7.88-7.85 (m, 1H), 7.77-7.67 (m, 1H), 7.67-7.64 (m, 1H), 7.56-7.53 (m, 2H), 7.40-7.23 (m, 3H), 7.05 (s, 1H), 6.82 (d, J=2.4, 1H)

m/z (CI method) 401 (M++1, 100%)

IR (KBr, cm-1) 1632.9, 1532.0,1484.4, 1406.4,1273.1, 1173.5, 1173.1, 767.2

Step (ii): *Synthesis of (4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine* **(E 23)**



E 23

Oxone (572 mg, 0.93 mmol) was added to a stirred solution of (4-methylsulfanyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine (125 mg, 0.31 mmol) in a mixture of acetone (3.0 mL) and water (1.5 mL), under a nitrogen atmosphere, at room temperature This reaction mixture was stirred at room temperature for about 3 hrs. After this time, ice-cold water was added to the mixture, and the resulting solid that formed was filtered off and dried. The product was further purified by column chromatography using $CHCl_3$ / hexane system (60 mg, 45%).

Melting range: 194-196 °C

^1H NMR (400 MHz, $CDCl_3$) δ 7.99-7.93 (m, 6H), 7.85 (d, J=7.8Hz, 1H), 7.76-7.72 (m, 1H), 7.47-7.43 (m, 1H), 7.11 (br s, D_2O exc, 1H, NH), 6.87 (d, J=2.4Hz, 1H), 3.07 (s, 3H).

IR (cm^{-1}): 1603, 1505, 1480

MS (m/z): 433 (M^+, 100%)

Example 24

Determination of Smooth muscle cell proliferation

Primary cultures of human aortic smooth muscle cells were obtained from Clonetics. SMC were initially grown in T-75 flasks prior to seeding in 96 well plates. The 96-well plates were seeded with 4000 cells/well. The following day cells were washed with serum free medium and left in serum free media for 24 hours for serum starvation. The next day cells received growth medium containing serum with or

without compound. The 24 h post treatment cell proliferation was assayed either assessing the incorporation of radiolabeled thymidine to DNA or using a non-radioactive cell proliferation kit from Promega (CellTiter AQ). Data are provided in the following table.

Table 13. Results of smooth muscle cell proliferation assay

Compound	Effect
E 8	77 % inhibition at 1 μM
E 16	50 % inhibition at 1.16 μM
E 11	50 % inhibition at 1 μM
E 18	50 % inhibition at 2.33 μM

Example 25

Inflammation assays

For inflammation assays, human aortic endothelial cells (HAECs) in 96 well plates were washed once with treatment medium (basal medium containing 1% FBS). Cells were treated with an inflammatory agent such as TNFα (0.5 ng/mL) or glycated human serum albumin (US Biologicals) as source of advanced glycation end products (AGEs) (300 μg/mL) for 18-24 h in the presence or absence of specified amount of compound. Cell supernatants were collected and used for measuring MCP-1 (monocyte chemoattractant protein 1) or IL-6 (interleukin-6) expression by ELISA. Cell layers were washed and used for determining vascular cell adhesion molecule-1 (VCAM-1) expression.

Example 26

MCP-1 ELISA (Enzyme-Linked Immunosorbent Assay)

MCP-1 ELISA was carried out using Quantikine Human MCP-1 kit as described by the manufacturer (R&D Systems, Inc.). Mouse anti-human MCP-1 was used as the capture antibody and HRP (horse radish peroxidase)-conjugated goat anti-human MCP-1 antibody was used as detection antibody. Culture medium was incubated with the capture antibody (in 96-well plate) for 2 h at room temperature.

Wells were washed three times with wash buffer (0.05% Tween-20 in PBS) followed by incubation with detection antibody for 2 h at room temperature. Color development was read at 45 nm in a microplate reader. Data are provided in the following table.

Table 14. Results of MCP-1 enzyme-linked immunosorbent assay

Compound	IC_{50} (μM)
E 8	2.1
E 7	5
E 13	5
E 15	4.2
E 23	9
E 19	1
E 21	0.43
E 22	0.75

Example 27

VCAM-1 ELISA

The cells were fixed cells with 100% methanol for 10min at room temperature. The methanol was removed and the plate was air-dried. 100 µl of 1:1000 diluted primary antibody (polyclonal goat anti-human VCAM-1 - R&D Systems #BBA19) was then added and incubated for 2 h at 37 C. The cells were washed with PBS and 100 µl of 1:5000 dilution of secondary antibody (rabbit anti-goat IgG-HRP - Zymed #81-1620) was added and incubated for 1h at room temperature. Cells were washed and 100 µl of substrate solution (R&D Systems# DY999) was added and incubated for 20 min in the dark at room temp. 50 µl of stop solution (2N sulfuric acid) was added to the wells and absorbency at 450 nm was noted. Data are provided in the following table.

Table 15. Results of VCAM-1 enzyme-linked immunosorbent assay

Compound	IC_{50} (μM)
E 8	3.6
E 13	3.5
E 15	5
E 23	8.1
E 19	1
E 21	0.61
E 22	2.1

Example 28

IL-6 ELISA

IL-6 expression in endothelial cell media were determined using DuaSet IL-6 ELISA kit from R&D Systems (Cat No DY206) as described by the manufacturer. Mouse anti-human IL-6 antibody was used as the capture antibody and biotinylated goat anti-human IL-6 was used as detection antibody. Culture medium was incubated with the capture antibody (in 96-well plate) for 2 h at room temperature. Wells were washed three times with wash buffer (0.05% Tween-20 in PBS) followed by incubation with detection antibody for 2 h at room temperature. The wells were then incubated with streptavidin HRP and color development was read at 450 nm in a microplate reader. Data are provided in the following table.

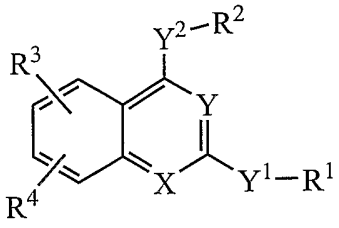
Table 16. Results of IL-6 enzyme-linked immunosorbent assay

Compound	IC_{50} (μM)
E 5	2

CLAIMS

We Claim:

1. A compound having the formula:



(I);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

X and Y are selected independently from CH or N, with a proviso that at least one of X or Y represents N;

Y^1 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl, alkoxy, or haloalkyl, any of which having up to 12 carbon atoms, halogen, or hydrogen;

R^5 is a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

any of R^1, R^2, and R^5 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, $-CO_2R^6$, $-COR^8$, $-CONR^6R^7$, $-SO_2R^8$ and $-SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or

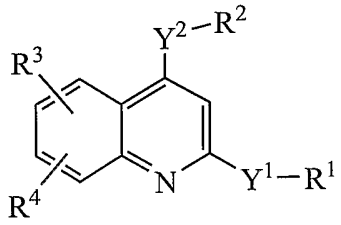
$>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

when R^3 and R^4 are selected independently from an alkyl, an alkoxy, or a haloalkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from an alkyl having up to 12 carbon atoms, hydroxyl, or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

2. A compound having the formula:



(II);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is $>NR^5$ or a direct a bond between the 6-membered ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the 6-membered ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl, alkoxy, or haloalkyl, any of which having up to 12 carbon atoms, halogen, or hydrogen;

R^5 is a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

any of R^1, R^2, and R^5 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a

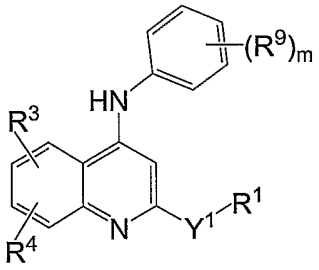
cycloalkyl, NR^6R^7, $-CO_2R^6$, $-COR^8$, $-CONR^6R^7$, $-SO_2R^8$ and $-SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

any of R^3 and R^4 is optionally substituted with at least one group selected independently from an alkyl having up to 12 carbon atoms, hydroxyl, or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

3. A compound according to Claim 2, having the formula:



(IIa);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

R^1 is a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^9, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a cycloalkyl, a haloalkoxy, any of which having up to 12 carbon atoms; or 2) halogen or hydroxyl;

m is an integer from 0 to 3, inclusive;

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, $CONR^6R^7$, $-SO_2R^8$, or $-SO_2NR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

4. A compound according to Claim 3, wherein:

Y^1 is a direct a bond between the heterocyclic ring and R^1;

m is an integer from 0 to 2, inclusive;

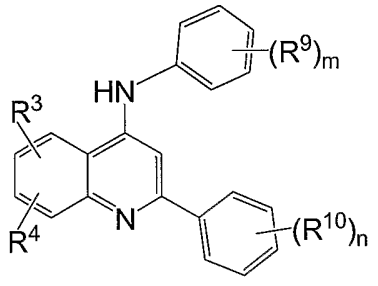
R^1 is a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$; and

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, $CONR^6R^7$, $-SO_2R^8$, or $-SO_2NR^6R^7$, any of which having up to 12 carbon atoms; or 2) halogen.

5. A compound according to Claim 3, wherein:

R^1 is a substituted or an unsubstituted heterocyclyl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6.

6. A compound according to Claim 2, having the formula:



(IIb),

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^9, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a cycloalkyl, a haloalkoxy, any of which having up to 12 carbon atoms; or 2) halogen or hydroxyl;

R^{10}, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an an alkylthio, a haloalkyl, a cycloalkyl, a haloalkoxy, SO_2R^8, $SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; or 2) halogen;

m and n are independently an integer from 0 to 3, inclusive;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

7. A compound according to Claim 6, wherein the compound is:

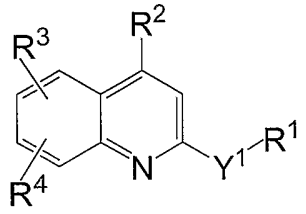
(3-chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine;

(3-chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine;

(4-chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine; or

any combination thereof.

8. A compound according to Claim 2, having the formula:



(IIc),

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, SO_2R^8, -$SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^2 is optionally substituted with at least one group selected independently from:

1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, -$SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-,

>S, or >NR^6, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

9. A compound according to Claim 8, wherein:

Y^1 is a direct a bond between the heterocyclic ring and R^1;

R^1 is a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6; and

R^2 is a substituted or an unsubstituted heteroaryl group having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6.

10. A compound according to Claim 9, wherein:

R^1 is a substituted or an unsubstituted heterocyclyl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6.

11. A compound according to Claim 8, wherein:

Y^1 is >NH; and

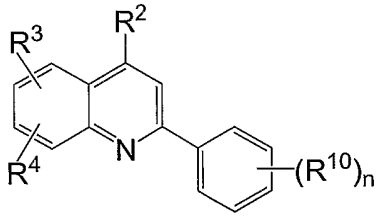
R^1 is selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6.

12. A compound according to Claim 11, wherein:

R^1 is a substituted or an unsubstituted heteroaryl having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$.

13. A compound according to Claim 8, wherein the compound is 2-benzo[1,3]-dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline.

14. A compound according to Claim 2, having the formula:



(IId);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^2 is selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^2 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, $-SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^{10}, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, $-SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

n is an integer from 0 to 2, inclusive;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

15. A compound according to Claim 14, wherein R^2 is a substituted or an unsubstituted pyrazole, imidazole or indole.

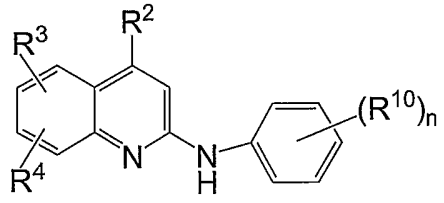
16. A compound according to Claim 14, wherein the compound is:

2-(4-fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline; or any combination thereof.

17. A compound according to Claim 2, having the formula:



(IIe);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^2 is a substituted or an unsubstituted heteroaryl having up to 12 carbon atoms, comprising at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from an alkyl having up to 12 carbon atoms, or hydrogen;

R^{10}, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, SO_2R^8, $-SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

n is an integer from 0 to 2, inclusive;

R^2 is optionally substituted with at least one group selected independently from:

1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, SO_2R^8, $-SO_2NR^6R^7$, or $CONR^6R^7$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

18. A compound according to Claim 17, wherein the compound is:

(4-methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine;

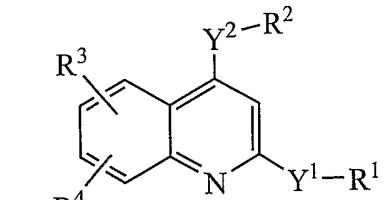
(4-trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine;

N-methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide;

N-methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide; or

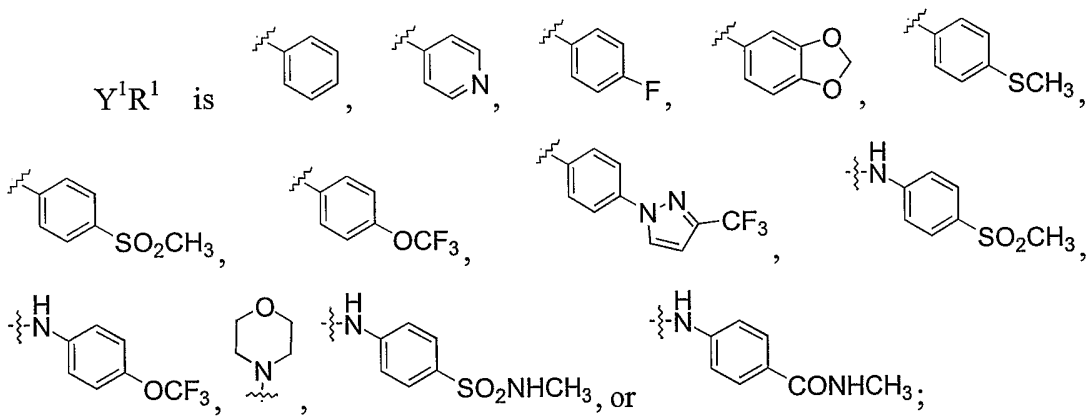
any combination thereof.

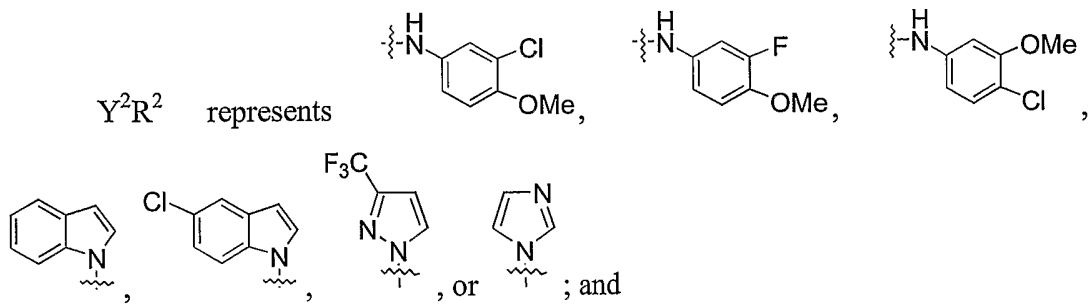
19. A compound according to Claim 2, having the formula:



17. (**II-1**);

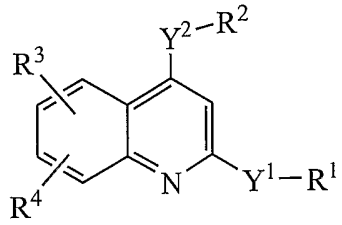
or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is 

Y^2R^2 represents 

R^3 and R^4 are hydrogen.

20. A composition comprising a pharmaceutically acceptable carrier and at least one compound having the formula:



(II),

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is $>NR^5$ or a direct a bond between the 6-membered ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the 6-membered ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl, heterocyclyl, or heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl or heterocyclyl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, $>NR^6$, $>SO_2$, or >CO;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl, alkoxy, or haloalkyl, any of which having up to 12 carbon atoms, halogen, or hydrogen;

R^5 is a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

any of R^1, R^2, and R^5 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, $-CO_2R^6$, $-COR^8$, $-CONR^6R^7$, $-SO_2R^8$ and $-SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen, hydroxyl, or cyano; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

any of R^3 and R^4 is optionally substituted with at least one group selected independently from an alkyl having up to 12 carbon atoms, hydroxyl, or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

21. The composition as claimed in Claim 20, further comprising:

optionally, a pharmaceutically acceptable auxiliary;

optionally, a pharmaceutically acceptable preservative;

optionally, a pharmaceutically acceptable excipient;

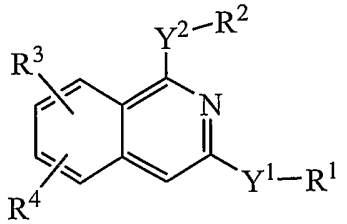
optionally, a pharmaceutically acceptable diluent; and

optionally, a pharmaceutically acceptable solvate.

22. The composition as claimed in Claim 21, further comprising an agent selected from an immunosuppressive agent, an anti-inflammatory agent, an antirheumatic agent, an antidyspilidemic agent, or any combination thereof.

23. The composition as claimed in Claim 21, wherein the composition is in the form of a tablet, a capsule, a cachet, a powder, a granule, a solution, a suspension, an emulsion, a bolus, a lozenge, a suppository, a pessary, a tampon, a cream, a gel, a paste, a foam, a spray, an aerosol, a microcapsule, a liposome, a transdermal patch, a pastille, a paste, or a mouthwash.

24. A compound having the formula:



(III),

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

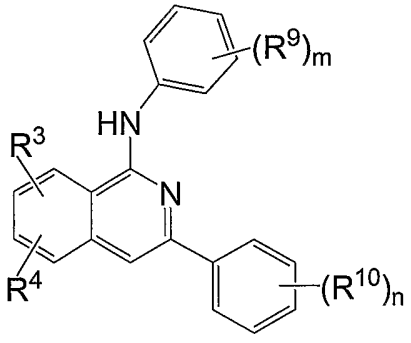
R^1 and R^2 are optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen;

R^8 is an alkyl or aryl having up to 12 carbon atoms; and

when R^3 or R^4 are independently an alkyl, R^3 or R^4 are optionally substituted with at least one group selected independently from hydroxyl or halogen.

25. A compound according to Claim 24, having the formula:



(IIIa),

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

R^9 and R^{10}, in each occurrence, are selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

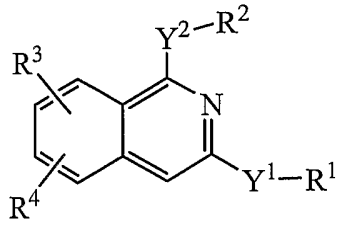
m and n are independently an integer from 0 to 3, inclusive;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

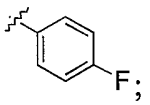
26. A compound according to Claim 24, wherein the compound is (3-fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine.

27. A compound according to Claim 24, having the formula:

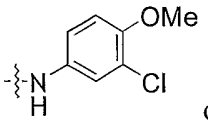
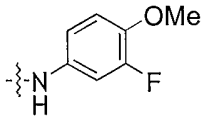


(III-1);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is 

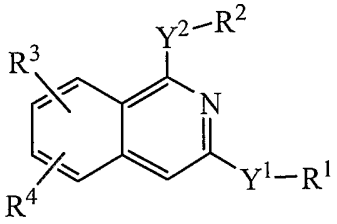
;

Y^2R^2 is  or  ;

R^3 is CH_3; and

R^4 is hydrogen.

28. A composition comprising a pharmaceutically acceptable carrier and at least one compound having the formula:


(III),

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^1;

Y^2 is $>NR^5$ or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

R^1 and R^2 are optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected

independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen;

R^8 is an alkyl or aryl having up to 12 carbon atoms; and

when R^3 or R^4 are independently an alkyl, R^3 or R^4 are optionally substituted with at least one group selected independently from hydroxyl or halogen.

29. The composition as claimed in Claim 28, further comprising:

optionally, a pharmaceutically acceptable auxiliary;

optionally, a pharmaceutically acceptable preservative;

optionally, a pharmaceutically acceptable excipient;

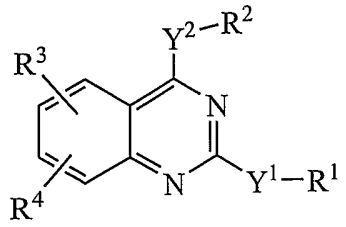
optionally, a pharmaceutically acceptable diluent; and

optionally, a pharmaceutically acceptable solvate.

30. The composition as claimed in Claim 29, further comprising an agent selected from an immunosuppressive agent, an anti-inflammatory agent, an antirheumatic agent, an antidyspilidemic agent, or any combination thereof.

31. The composition as claimed in Claim 29, wherein the composition is in the form of a tablet, a capsule, a cachet, a powder, a granule, a solution, a suspension, an emulsion, a bolus, a lozenge, a suppository, a pessary, a tampon, a cream, a gel, a paste, a foam, a spray, an aerosol, a microcapsule, a liposome, a transdermal patch, a pastille, a paste, or a mouthwash.

32. A compound having the formula:



(IV);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

Y^2 is >NH or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms; wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

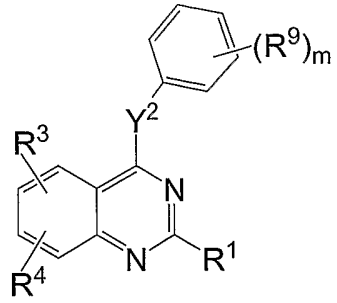
R^1 and R^2 are optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

when R^3 and R^4 are selected independently from an alkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from hydroxyl or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

33. A compound according to Claim 32, having the formula:



(IVa);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^2 is >NH or a direct a bond between the heterocyclic ring and R^2;

R^1 is a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$;

R^9, in each occurrence, is selected independently from: 1) an alkyl, an alkoxy, or a haloalkoxy, any of which having up to 12 carbon atoms; or 2) halogen or hydroxyl;

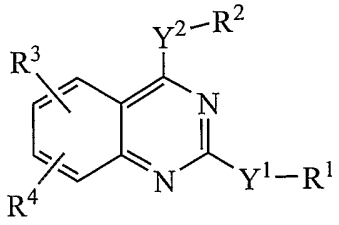
m is an integer from 0 to 2, inclusive;

R^1 is optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or $>NR^6$, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen; and

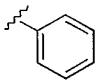
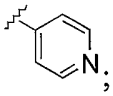
when R^3 and R^4 are selected independently from an alkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from hydroxyl, or halogen.

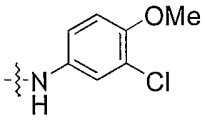
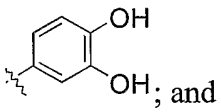
34. A compound according to Claim 32, having the formula:



(IV-1);

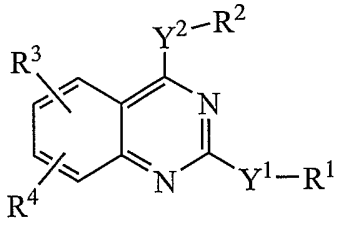
or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1R^1 is  or  ;

Y^2R^2 is  or  ; and

R^3 and R^4 are hydrogen.

35. A composition comprising a pharmaceutically acceptable carrier and at least one compound having the formula:



(IV);

or a salt, a prodrug, a diastereomeric mixture, an enantiomer, a tautomer, a racemic mixture thereof, or any combination thereof, wherein:

Y^1 is >NH or a direct a bond between the heterocyclic ring and R^1;

Y^2 is >NH or a direct a bond between the heterocyclic ring and R^2;

R^1 and R^2 are selected independently from a substituted or an unsubstituted aryl or a substituted or an unsubstituted heteroaryl, any of which having up to 12

carbon atoms; wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6;

R^3 and R^4 are selected independently from a substituted or an unsubstituted alkyl having up to 12 carbon atoms, or hydrogen;

R^1 and R^2 are optionally substituted with at least one group selected independently from: 1) an alkyl, an alkoxy, an alkylthio, a haloalkyl, a haloalkoxy, a cycloalkyl, NR^6R^7, CO_2R^6, COR^8, $CONR^6R^7$, SO_2R^8, $SO_2NR^6R^7$, $NHSO_2R^8$, or $NHCOR^8$, any of which having up to 12 carbon atoms; 2) halogen or hydroxyl; or 3) a substituted or an unsubstituted aryl, or a substituted or an unsubstituted heteroaryl, any of which having up to 12 carbon atoms, wherein any heteroaryl comprises at least one heteroatom or heterogroup selected from >O, >N-, >S, or >NR^6, and wherein the aryl and the heteroaryl are optionally substituted with at least one group selected independently from an alkyl, an alkoxy, or a haloalkyl, any of which having up to 12 carbon atoms;

when R^3 and R^4 are selected independently from an alkyl, then R^3 and R^4 are optionally substituted with at least one group selected independently from hydroxyl or halogen;

R^6 and R^7 are selected independently from an alkyl or an aryl having up to 12 carbon atoms, or hydrogen; and

R^8 is an alkyl or aryl having up to 12 carbon atoms.

36. The composition as claimed in Claim 35, further comprising:
optionally, a pharmaceutically acceptable auxiliary;
optionally, a pharmaceutically acceptable preservative;
optionally, a pharmaceutically acceptable excipient;
optionally, a pharmaceutically acceptable diluent; and
optionally, a pharmaceutically acceptable solvate.

37. The composition as claimed in Claim 36, further comprising an agent selected from an immunosuppressive agent, an anti-inflammatory agent, an antirheumatic agent, an antidyspilidemic agent, or any combination thereof.

38. The composition as claimed in Claim 36, wherein the composition is in the form of a tablet, a capsule, a cachet, a powder, a granule, a solution, a suspension, an emulsion, a bolus, a lozenge, a suppository, a pessary, a tampon, a cream, a gel, a paste, a foam, a spray, an aerosol, a microcapsule, a liposome, a transdermal patch, a pastille, a paste, or a mouthwash.

39. A compound selected from:

(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine;

(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine;

4-(2-Pyridin-4-yl-quinazolin-4-yl)-benzene-1,3-diol;

4-(2-Phenyl-quinazolin-4-yl)-benzene-1,3-diol;

(3-Chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine;

(3-Chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine;

(3-Fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine;

(3-Chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine;

4-Indol-1-yl-2-phenyl-quinoline;

4-(5-Chloro-indol-1-yl)-2-phenyl-quinoline;

2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

4-(3-Trifluoromethyl-pyrazol-1-yl)-2-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-quinoline;

(4-Chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine;

2-(4-Fluoro-phenyl)-4-imidazol-1-yl-quinoline;

2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

(4-Trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine;

2-Morpholin-4-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide;

N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide;

(4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine; or

any combination thereof.

40. A composition comprising a pharmaceutically acceptable carrier and at least one compound selected from:

(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinolin-4-yl)-amine;

(3-Chloro-4-methoxy-phenyl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine;

4-(2-Pyridin-4-yl-quinazolin-4-yl)-benzene-1,3-diol;

4-(2-Phenyl-quinazolin-4-yl)-benzene-1,3-diol;

(3-Chloro-4-methoxy-phenyl)-(2-phenyl-quinolin-4-yl)-amine;

(3-Chloro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine;

(3-Fluoro-4-methoxy-phenyl)-[3-(4-fluoro-phenyl)-7-methyl-isoquinolin-1-yl]-amine;

(3-Chloro-4-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine;

4-Indol-1-yl-2-phenyl-quinoline;

4-(5-Chloro-indol-1-yl)-2-phenyl-quinoline;

2-(4-Fluoro-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

4-(3-Trifluoromethyl-pyrazol-1-yl)-2-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-quinoline;

(4-Chloro-3-methoxy-phenyl)-[2-(4-fluoro-phenyl)-quinolin-4-yl]-amine;

2-(4-Fluoro-phenyl)-4-imidazol-1-yl-quinoline;

2-Benzo[1,3]dioxol-5-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-Methylsulfanyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-Methanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

2-(4-Trifluoromethoxy-phenyl)-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

(4-Trifluoromethoxy-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine;

2-Morpholin-4-yl-4-(3-trifluoromethyl-pyrazol-1-yl)-quinoline;

N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzenesulfonamide;

N-Methyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-ylamino]-benzamide;

(4-Methanesulfonyl-phenyl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-quinolin-2-yl]-amine; or

any combination thereof.

41. The composition as claimed in Claim 40, further comprising:

optionally, a pharmaceutically acceptable auxiliary;

optionally, a pharmaceutically acceptable preservative;

optionally, a pharmaceutically acceptable excipient;

optionally, a pharmaceutically acceptable diluent; and

optionally, a pharmaceutically acceptable solvate.

42. The composition as claimed in Claim 41, further comprising an agent selected from an immunosuppressive agent, an anti-inflammatory agent, an antirheumatic agent, an antidyspilidemic agent, or any combination thereof.

43. The composition as claimed in Claim 41, wherein the composition is in the form of a tablet, a capsule, a cachet, a powder, a granule, a solution, a suspension, an emulsion, a bolus, a lozenge, a suppository, a pessary, a tampon, a cream, a gel, a paste, a foam, a spray, an aerosol, a microcapsule, a liposome, a transdermal patch, a pastille, a paste, or a mouthwash.

44. A method of treating a condition or disease state mediated by a high expression of TNF-alpha in a human or an animal, comprising administering an effective amount of at least one compound according to Claim 1 to the human or the animal, sufficient to reduce TNF-alpha levels.

45. A method of treating a condition or disease state mediated by an increased proliferation of smooth muscle cells in a human or an animal, comprising administering an effective amount of at least one compound according to Claim 1 to the human or the animal, sufficient to reduce smooth muscle cell proliferation.

46. A method of treating atherosclerosis, arthritis, restenosis, diabetic nephropathy, or dyslipidemia in a human or an animal, comprising administering an effective amount of at least one compound according to Claim 1.