PP028218.0002 (20366-156WO1)

QUINAZOLINES FOR PDK1 INHIBITION

FIELD OF THE INVENTION

The present invention generally relates to small molecule inhibitors of 3-phosphoinositide-dependent kinase (PDK1). In some embodiments, the compounds can be used as therapeutics in the treatment of cellular proliferative diseases.

BACKGROUND OF THE INVENTION

PDK1 (3-Phopsphoinositide-dependent kinase 1) is a serine/threonine kinase belonging to the AGC kinase super family. PDK1 was first identified as the upstream kinase responsible for activating protein kinase B/AKT in the presence of phosphoinositide lipids (PIP_3). PDK1 activates AKT by phosphorylating a specific residue (threonine 308) located in the activation loop of this kinase. Subsequent research has shown that PDK1 is responsible for phosphorylating the activation-loop of many AGC kinases including p90 ribosomal S6 kinase (RSK), protein kinase C family members (PKC), p70 ribosomal S6 kinase (70S6K), and the serum and glucocorticoid-induced protein kinase (SGK). Thus, PDK1 is a central activator of multiple signaling pathways that are involved in cell proliferation, survival and control of apoptosis. Importantly, alterations in these signaling pathways are frequently observed in a variety of human cancers. For example, AKT is highly activated in a large percentage of common tumor types including melanoma, breast, lung, prostate and ovarian cancers. RSK levels are elevated in prostate cancers, and an RSK-specific inhibitor (SL0101) has recently been shown to inhibit the proliferation of multiple prostate cancer cell lines. Similarly, PKCε has been shown to play an important role in regulating apoptosis and promoting survival of glioma cells.

The human PDK1 gene encodes a 556 amino acid protein with an amino-terminal catalytic domain and a non-catalytic carboxy terminal containing a pleckstrin homology domain (PH). Recent studies suggest that PDK1 is a constitutively active kinase, and that PDK1 regulation occurs through the localization or conformational state of PDK1 target proteins. For example, the PH domain of PDK1 is required for the binding of PIP_3 lipids produced by PI3kinase (PI3K). PDK1 binding of PIP_3 lipids results in membrane co-

localization with AKT, another PH domain containing protein. Once co-localized, PDK1 activates AKT by phosphorylating threonine308. Alternatively, PDK1 can activate other AGC kinases independent of PIP_3 lipids by binding directly to a conserved motif found on these targets. Because PDK1 regulates two distinct classes of downstream signaling substrates (PI3K-dependent and independent targets), inhibitors of this enzyme could have important therapeutic value in a variety of human cancers. For instance, PDK1 inhibitors could be efficacious in tumors in which the PI3K signaling pathway is upregulated due to activating mutations, amplification of PI3K itself or its upstream receptor tyrosine kinases, or deletion of PTEN, the phosphatase the counteracts PI3K activity. The finding that mice expressing half the normal amount of PTEN are protected from developing a wide range of tumors by reducing PDK1 expression levels supports this idea. Alternatively, PDK1 inhibitors could be useful in treating cancers driven by PIP_3-independent PDK1 signaling pathways (e.g. K-ras or H-ras driven cancers).

Finally, the recent identification of PDK1 mutations ($PDK1^{T354M}$, $PDK1^{D527E}$) in human colorectal cancers suggests that inhibitors of this kinase may have therapeutic value by directly inhibiting either wild-type or mutant forms of this protein. See, Parsons *et al.*, *Nature* 436, 792 (11 August 2005) "Colorectal cancer: Mutations in a signaling pathway."

In summary, PDK1 is a central activator of several signaling pathways that are frequently altered in human cancers making it an attractive target for therapeutic intervention.

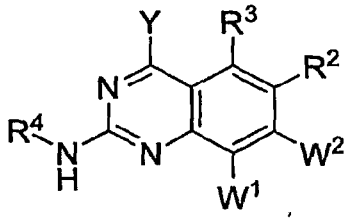
U.S. Patent No. 6,982,260 discloses quinazoline compounds for inhibition of cyclin-dependent kinases, and International Application PCT/IB2004/000091 discloses 2-aminopyridine substituted heterocycles as inhibitors for cellular proliferation.

This invention is directed to the discovery of novel compounds for PDK1 inhibition and use of these compounds to treat a variety of diseases or disorders involving cellular proliferation.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention provides PDK1, Cdk1, and/or Cdk2 inhibitors that are useful as therapeutic agents, for the treatment of diseases and disorders characterized by abnormal cellular proliferation, for example cancers of the prostate, lung, colon, breast, among others.

In some embodiments, the instant invention provides compounds that have the Formula I:



I

wherein,

one of W^1 or W^2 is R^1 and the other is $-L-A^1$;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl;

A^1 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, or substituted heterocyclyl;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

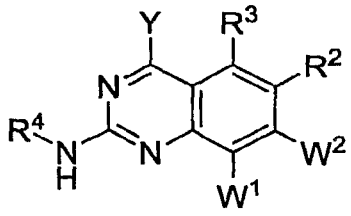
R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl,

substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

provided when R^4 is heteroaryl or substituted heteroaryl, W^2 is not aryl or heteroaryl; or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In some further embodiments, the compounds of the invention have the Formula I:



I

wherein:

one of W^1 or W^2 is R^1 and the other is $-L-A^1$;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl;

A^1 is hydroxyl, amino, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cyclyl, or substituted cyclyl, heterocyclyl, or substituted heterocyclyl, provided whenW^2 is hydroxyl or methoxy, A^1 is not isopropyl or cyclopentyl;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

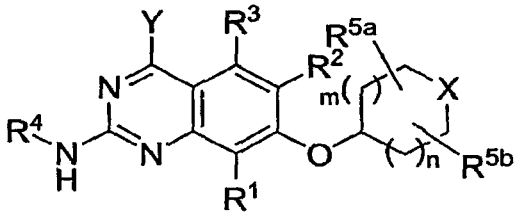
R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In some further embodiments, compounds of the invention have the Formula II:



II

wherein:

X is O or NR^6;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^{5a} and R^{5b} are each independently H, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, or substituted amino;

R^6 is H, acyl, substituted carbonyl, sulfonyl, alkyl, or substituted alkyl;

or R^{5a} and R^6 are taken together to form a bridging alkylene moiety;

or R^{5a} and R^{5b} are taken together to form a bridging alkylene moiety;

m and n are independently 0, 1 or 2;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl,

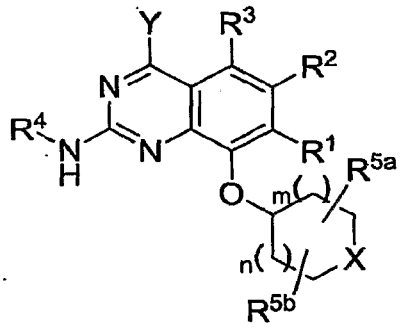
sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In some further embodiments, the compounds of the invention have the Formula III:



III

wherein,

X is O or NR^6;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^{5a} and R^{5b} are each independently H, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, or substituted amino;

R^6 is H, acyl, substituted carbonyl, sulfonyl, alkyl, or substituted alkyl;

or R^{5a} and R^6 are taken together to form a bridging alkylene moiety;

or R^{5a} and R^{5b} are taken together to form a bridging alkylene moiety;

m and n are independently 0, 1 or 2;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In some further embodiments, the invention provides compositions, preferably pharmaceutical compositions, that contain one or more compounds of the invention. In further embodiments, the invention provides methods of treating diseases or disorders that are characterized by, *inter alia*, abnormal cellular proliferation, for example cancer and/or precancerous lesions, that employ compounds of the invention. The invention further provides methods of inhibiting tumor cell growth in a subject, that employ compounds of the invention. The invention further provides methods of manufacturing compounds and compositions described herein, and method for the use of the quinazolines of the invention in methods for manufacturing medicaments for use in the methods of the invention. In each of the embodiments of the invention, compounds, such as those of Formula I, can be used in the manufacture of a medicament for inhibiting PDK1.

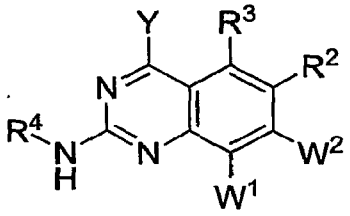
In further embodiments, the invention provides the use of the compounds of the invention, in the manufacture of medicament for PDK1 inhibition, and/ or for treatment of one or more of the aforementioned diseases or disorders.

Further embodiments of the invention include those described in the detailed description.

DETAILED DESCRIPTION

In accordance with the present invention, Applicants have discovered novel quinazoline PDK1 inhibitors that will provide effective treatments for disorders such as those described herein and those apparent to one skilled in the art.

In some embodiments, the present invention provides compounds that have the Formula I:



I

wherein,

one of W^1 or W^2 is R^1 and the other is $-L-A^1$;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl;

A^1 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, or substituted heterocyclyl;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted

heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

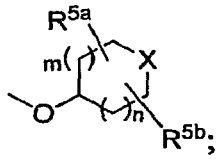
R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

The quinazoline compounds of this invention inhibit of PDK1 activity or inhibit cell proliferation. In some embodiments, the quinazoline compounds have low IC_{50} values with regard to inhibition of PDK1 activity (i.e., the concention of a compound that is required for 50% inhibition of PDK1 activity) or low EC_{50} with regard to inhibition of cell proliferation (i.e., the concentration of a compound which is required to induce inhibitory response against cell proliferation halfway between the baseline and maximum). For example, some quinazoline compounds exhibit IC_{50} or EC_{50} valaues of about 25 μM or less, about 10 μM or less, about 1 μM or less, or about 0.1 μM or even less according to the PDK1 kinase alpha screen assay and cell proliferation described herein.

In more particular embodiments, $-L-A^1$ is a heterocyclyloxy group having the structure:



wherein,

X is O or NR^6;

R^{5a} and R^{5b} are each independently H, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, or substituted amino;

R^6 is H, acyl, substituted carbonyl, sulfonyl, alkyl, or substituted alkyl;

or R^{5a} and R^6 are taken together to form a bridging alkylene moiety;

or R^{5a} and R^{5b} are taken together to form a bridging alkylene moiety;

m and n are independently 0, 1 or 2.

In a more particular embodiment W^1 is $-L-A^1$.

In another more particular embodiment W^2 is $-L-A^1$.

In some embodiments, R^4 is substituted phenyl.

In some embodiments, R^4 is phenyl substituted with a group of formula $-X^1-N(R_{501})(R_{502})$; wherein X^1 is SO_2 or C(=O); and R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino. In some such embodiments, X^1 is SO_2. In some such embodiments, $-N(R_{501})(R_{502})$ forms $-NH_2$, -NH-alkyl, -NH-alkyl substituted with alkoxy, -NH-cycloalkyl, morpholino, -NH-(alkyl)-pyrrolidinyl or piperizinyl optionally substituted with alkyl. In some further such embodiments,

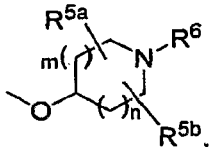
$-N(R_{501})(R_{502})$ forms $-NH_2$, $-NH-CH(CH_3)_2$, $-NH-(CH_2)_2-O-CH_3$, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or $-NH-(CH_2)_2$-pyrrolidin-1-yl.

In some embodiments, R^4 is substituted phenyl and X^1 is C(=O). In some such embodiments, $-N(R_{501})(R_{502})$ forms $-NH_2$, -NH-alkyl, -NH-alkyl substituted with alkoxy, or -NH-cycloalkyl.

In some embodiments, R^2 is H or halogen.

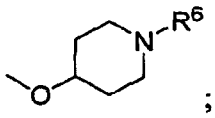
In some embodiments, R^3 is H.

In some further embodiments, W^2 is H, halogen, cyano, heteroaryl, substituted heteroaryl, phenyl, substituted phenyl, or a group of formula:



In some further embodiments, W^2 is H, halogen, cyano; or phenyl optionally substituted with–C(=O) $-N(R^{501})(R^{502})$; or a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms independently selected from O, S and N, that is optionally substituted with up

to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; or a group of formula:



;

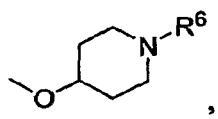
wherein each R_{501} and each R_{502} is independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl.

In some embodiments, W^2 is H, halogen or cyano. In some further embodiments, W^2 is phenyl optionally substituted with $-C(=O)-N(R^{501})(R^{502})$; wherein R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino. In some such embodiments, R^{501} and R^{502} are each independently selected from H and alkyl.

In some embodiments, W^2 is a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms independently selected from O, S and N, that is optionally substituted with up to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; wherein R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

In some further embodiments, W^2 is a heteroaryl group selected from pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl and thiazolyl, the heteroaryl group being optionally substituted with up to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; wherein R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino. In some such embodiments, R^{501} and R^{502} are each independently selected from H and alkyl.

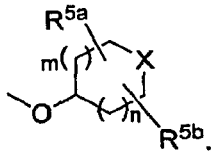
In some embodiments, W^2 is a group of formula:



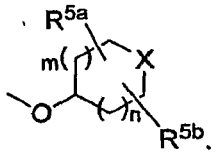
,

wherein R^6 is H or alkyl.

In some embodiments, W^1 is H, heteroaryl, substituted heteroaryl, or a group of formula:



In some such embodiments, W^1 is a group of formula:



In some such embodiments, X is NR^6. In further such embodiments, X is NR^6, R^{5b} is H, and R^6 and R^{5b} together form an alkylene bridge, for example $-(CH_2)_2-$.

In some embodiments, X is NR^6, and R^{5a} and R^{5b} together form an alkylene bridge, for example $-(CH_2)_2-$. In some embodiments, X is NR^6, and R^6 is H or alkyl. In some embodiments, X is NR^6, m and n are each 1, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, X is NR^6, m is 1 and n is 0, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, X is NR^6, m is 2 and n is 0, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, X is NR^6, m and n are each 0, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

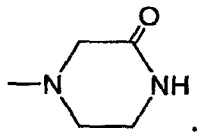
In some embodiments, Y is H or C_{1-3} alkyl. In other embodiments Y is H or $-CH_3$. In more particular embodiments, Y is H.

In some embodiments, W^1 is heteroaryl or substituted heteroaryl. In some further embodiments, W^1 is heteroaryl selected from pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl and thiazolyl, the heteroaryl group being optionally substituted with up to three substituents selected from alkyl, alkoxy, $-N(R^{501})(R^{502})$ and heterocyclyl; wherein R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is

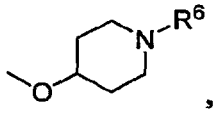
optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

In some embodiments, W^1 is pyridinyl optionally substituted with up to three substituents selected from alkyl, alkoxy, $-N(R^{501})(R^{502})$ and heterocyclyl; wherein R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

In some embodiments, W^1 is pyridinyl optionally substituted with heterocyclyl, for example a group of formula:

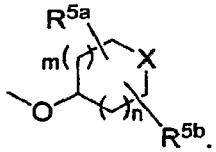


In some embodiments, W^2 is H, halogen, cyano, phenyl optionally substituted with–C(=O) $-N(R^{501})(R^{502})$; or heteroaryl selected from pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl and thiazolyl, the heteroaryl group being optionally substituted with up to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; or a group of formula:

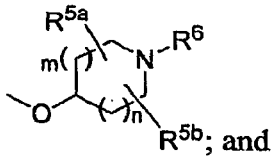


wherein R^6 is H or alkyl; and R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R_{501} and R_{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

In some embodiments, W^1 is pyridinyl optionally substituted with up to three substituents selected from alkyl, alkoxy, $-N(R^{501})(R^{502})$ and heterocyclyl; or W^1 is a group of formula:

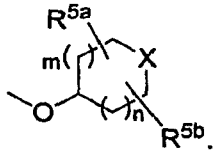


In some further embodiments, R_4 is substituted phenyl; W^2 is H, halogen, cyano, heteroaryl, substituted heteroaryl, phenyl, substituted phenyl, or a group of formula:



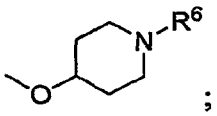
; and

W^1 is H, heteroaryl, substituted heteroaryl, or a group of formula:



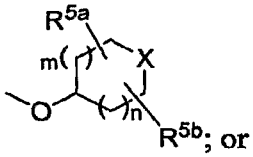
.

In some still further embodiments, R_4 is phenyl substituted with a group of formula $-X_1-N(R^{501})(R^{502})$; wherein X_1 is SO_2 or C(=O); and R^{501} and R^{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and a group of formula –alkyl-heterocyclyl; or R^{501} and R^{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl; W^2 is H, halogen, cyano; or phenyl optionally substituted with–C(=O) $-N(R^{501})(R^{502})$; or a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms independently selected from O, S and N, that is optionally substituted with up to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; or a group of formula:



;

W^1 is a group of formula:

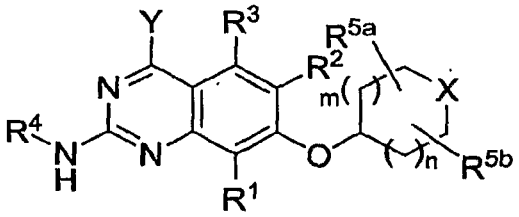


; or

heteroaryl selected from pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl and thiazolyl, the heteroaryl group being optionally substituted with up to three substituents selected from alkyl, alkoxy, $-N(R^{501})(R^{502})$ and heterocyclyl; wherein each R^{501} and each R^{502} is independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl.

In some embodiments of each of the foregoing, R^2 is H or halogen, and R^3 is H.

In some embodiments, compounds of the invention have the Formula II:



II

wherein:

X is O or NR^6;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^{5a} and R^{5b} are each independently H, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, or substituted amino;

R^6 is H, acyl, substituted carbonyl, sulfonyl, alkyl, or substituted alkyl;

or R^{5a} and R^6 are taken together to form a bridging alkylene moiety;

or R^{5a} and R^{5b} are taken together to form a bridging alkylene moiety;

m and n are independently 0, 1 or 2;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted

alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In some embodiments, R^4 is substituted phenyl. In some such embodiments, R^4 is phenyl substituted with a group of formula $-X_1$-$N(R^{501})(R^{502})$; wherein X_1 is SO_2 or C(=O); and R^{501} and R^{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R^{501} and R^{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl. In some such embodiments, X^1 is SO_2. In some further such embodiments, $-N(R^{501})(R^{502})$ forms $-NH_2$, -NH- alkyl, -NH-alkyl substituted with alkoxy, -NH-cycloalkyl, morpholino, -NH-(alkyl)-pyrrolidinyl or piperizinyl optionally substituted with alkyl. In some further embodiments, $-N(R^{501})(R^{502})$ forms $-NH_2$, $-NH-CH(CH_3)_2$, $-NH-(CH_2)_2-O-CH_3$, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or $-NH-(CH_2)_2$-pyrrolidin-1-yl.

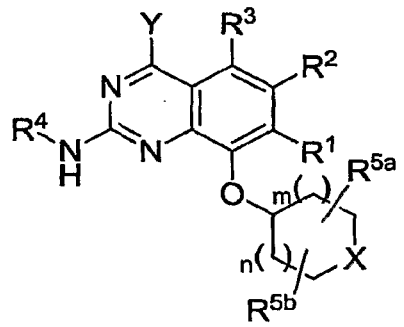
In some of the foregoing embodiments, X^1 is C(=O). In some such embodiments, $-N(R^{501})(R^{502})$ forms $-NH_2$, -NH-alkyl, -NH-alkyl substituted with alkoxy, or -NH-cycloalkyl.

In some embodiments, Y is H or C_{1-3} alkyl. In other embodiments Y is H or $-CH_3$. In more particular embodiments, Y is H.

In some embodiments, R^2 is H or halogen. In some further embodiments, R^3 is H.

In some embodiments, R^1 is selected from H, alkyl, and substituted alkyl.

In some embodiments, compounds of the invention have the Formula III:



III

wherein,

X is O or NR^6;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^{5a} and R^{5b} are each independently H, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, or substituted amino;

R^6 is H, acyl, substituted carbonyl, sulfonyl, alkyl, or substituted alkyl;

or R^{5a} and R^6 are taken together to form a bridging alkylene moiety;

or R^{5a} and R^{5b} are taken together to form a bridging alkylene moiety;

m and n are independently 0, 1 or 2;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In some such embodiments, R^4 is substituted phenyl. In some such embodiments, R^4 is phenyl substituted with a group of formula $-X_1\text{-}N(R^{501})(R^{502})$; wherein X_1 is SO_2 or C(=O); and R^{501} and R^{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl; or R^{501} and R^{502}, taken together, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from

C_{1-3} alkyl. In some such embodiments, X^1 is SO_2. In some such embodiments, -$N(R^{501})(R^{502})$ forms -NH_2, -NH-alkyl, -NH-alkyl substituted with alkoxy, -NH-cycloalkyl, morpholino, -NH-(alkyl)-pyrrolidinyl or piperizinyl optionally substituted with alkyl. In some further embodiments, -$N(R^{501})(R^{502})$ forms -NH_2, -NH-$CH(CH_3)_2$, -NH-$(CH_2)_2$-O-CH_3, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or -NH-$(CH_2)_2$-pyrrolidin-1-yl.

In of the foregoing some embodiments, X^1 is C(=O). In some such embodiments, -$N(R^{501})(R^{502})$ forms -NH_2, -NH-alkyl, -NH-alkyl substituted with alkoxy, or -NH-cycloalkyl.

In some embodiments, R^2 is H or halogen. In some further embodiments, R^3 is H.

In some embodiments, X is NR^6.

In some embodiments, X is NR^6, R^{5b} is H, and R^6 and R^{5b} together form an alkylene bridge, for example -$(CH_2)_2$-.

In some embodiments, X is NR^6, and R^{5a} and R^{5b} together form an alkylene bridge, for example -$(CH_2)_2$-.

In some embodiments, X is NR^6, wherein R^6 is H or alkyl.

In some embodiments, X is NR^6, m and n are each 1, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, X is NR^6, m is 1 and n is 0, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, X is NR^6, m is 2 and n is 0, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, X is NR^6, m and n are each 0, and R^{5a} and R^{5b} are each H. In some such embodiments, R^6 is H or alkyl.

In some embodiments, Y is H or C_{1-3} alkyl. In other embodiments Y is H or $-CH_3$. In more particular embodiments, Y is H.

In some embodiments of the compounds of Formula III, R^1 is selected from H, halogen, cyano, heteroaryl, substituted heteroaryl, phenyl, and substituted phenyl. In some further embodiments, R^1 is H, halogen, cyano; or phenyl optionally substituted with–C(=O) – $N(R^{501})(R^{502})$; or a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms independently selected from O, S and N, that is optionally substituted with up to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; wherein each R_{501} and each R_{502} is independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl. In some such embodiments, R^1 is phenyl optionally substituted with–

C(=O) –N(R^{501})(R^{502}). In some such embodiments, R^{501} and R^{502} are each independently selected from H and alkyl.

In some further embodiments, R^1 is H, halogen or cyano.

In some of the foregoing embodiments, R^1 is a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms independently selected from O, S and N, that is optionally substituted with up to three substituents selected from alkyl, alkoxy and –N(R^{501})(R^{502}).

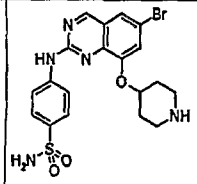
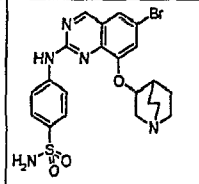
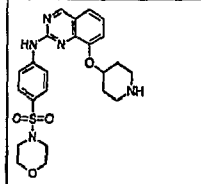
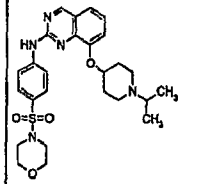
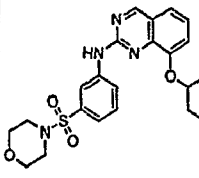
In some of the foregoing embodiments, R^1 is a heteroaryl group selected from pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl and thiazolyl, the heteroaryl group being optionally substituted with up to three substituents selected from alkyl, alkoxy and –N(R^{501})(R^{502}). In some such embodiments, R^{501} and R^{502} are each independently selected from H and alkyl.

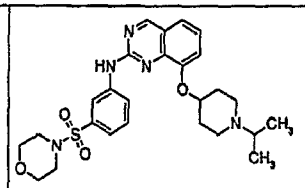
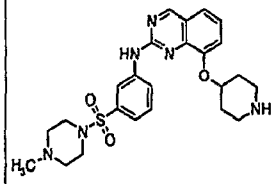
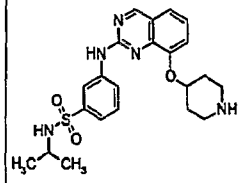
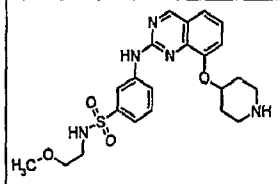
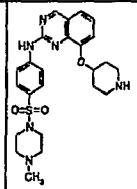
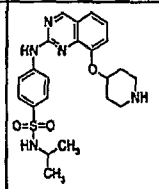
In some of each of the foregoing embodiments, R^4 is other than pyridinyl. In some of each of the foregoing embodiments, R^4 is other than pyridin-2-yl.

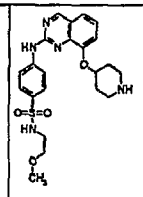
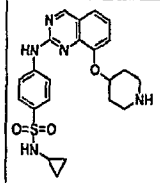
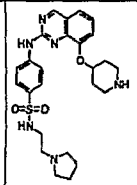
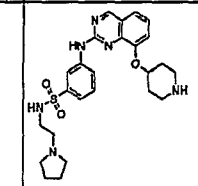
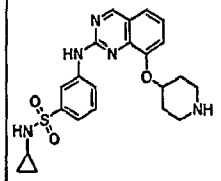
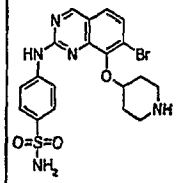
Some compounds of the invention are shown in Tables 1-5 below. Physical data is provided in the column marked "MS (M+1)..." for each of the compounds, as is retention time data.

The columns labeled "PDK1 IC_{50}" "CPEC50 A2780," "CPEC50 PC3," and "CPEC50 PC3MM" indicates the compound's activity in the PDK1 Kinase Alpha Screen Assay and the Cell Proliferation Assay described below. The symbol "+" indicates IC_{50} values or EC_{50} values of 25 μM or greater (or compounds not evaluated), the symbol "++" indicates IC_{50} values or EC_{50} values between less than 25 μM and greater than 10 μM, the symbol "+++" indicates IC_{50} values or EC_{50} values of 10 μM or less and greater than 5 μM, and the symbol "++++" indicates IC_{50} values or EC_{50} values less than 5 μM.

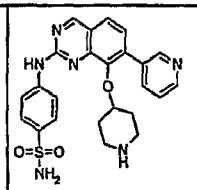
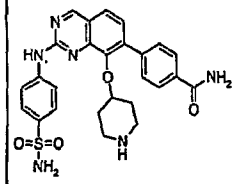
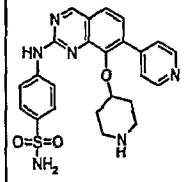
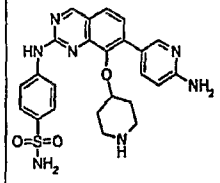
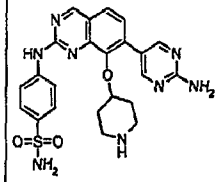
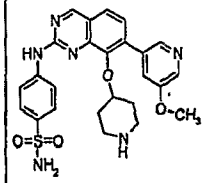
Table 1

Compound	Structure	Name	LC/MS (M+1(m/z), Rt(min))	PDK1 IC_{50}	$CPEC_{50}$ A2780	$CPEC_{50}$ PC3	$CPEC_{50}$ PC3MM	PAKT308 PC3 IC_{50}
1		4-[6-Bromo-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	578/580, 2.03	++++	++++	++++		+++
2		4-[8-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-6-bromo-quinazolin-2-ylamino]-benzenesulfonamide	504/506, 2.07	++++	++++	++++		++++
3		[4-(Morpholine-4-sulfonyl)-phenyl]-[8-(piperidin-4-yloxy)-quinazolin-2-yl]-amine	470.0, 2.14	++++	++++	++++		++++
4		[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-[4-(morpholine-4-sulfonyl)-phenyl]-amine	512.1, 2.26	++++	++++	++++		++++
5		[3-(Morpholine-4-sulfonyl)-phenyl]-[8-(piperidin-4-yloxy)-quinazolin-2-yl]-amine	470.1, 2.11	++++	++++			+++

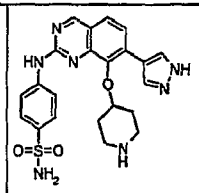
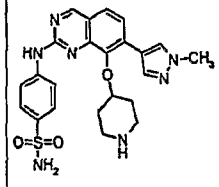
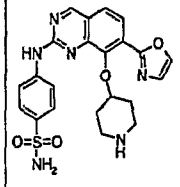
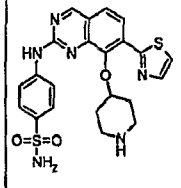
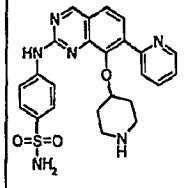
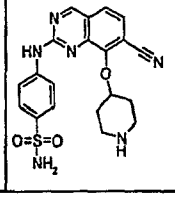
6		[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-[3-(morpholine-4-sulfonyl)-phenyl]-amine	512.1, 2.24	++++	++++			
7		[3-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-[8-(piperidin-4-yloxy)-quinazolin-2-yl]-amine	483.1, 1.80	++++	++++			
8		N-Isopropyl-3-[8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	442.1, 2.17	++++	++++			
9		N-(2-Methoxy-ethyl)-3-[8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	458.1, 2.02	++++	++++			
10		[4-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-[8-(piperidin-4-yloxy)-quinazolin-2-yl]-amine	483.1, 1.84	++++	++++			
11		N-Isopropyl-4-[8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	442.1, 2.16	++++	++++	++++		++++

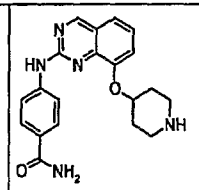
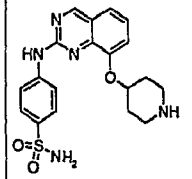
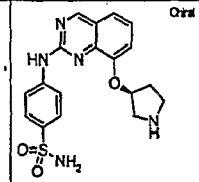
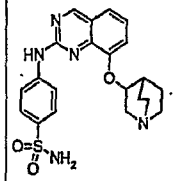
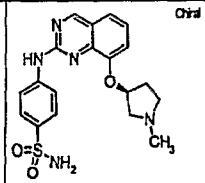
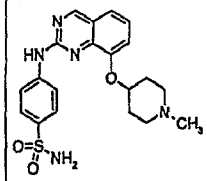
12		N-(2-Methoxy-ethyl)-4-[8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	458.1, 2.03	++++	++++	++++		++++
13		N-Cyclopropyl-4-[8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	440.1, 2.12	++++	++++	++++		++++
14		4-[8-(Piperidin-4-yloxy)-quinazolin-2-ylamino]-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide	497.1, 1.85	++++	++++	++++		+++
15		3-[8-(Piperidin-4-yloxy)-quinazolin-2-ylamino]-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide	497.1, 1.80	++++	+++			
16		N-Cyclopropyl-3-[8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	440.1, 2.10	++++	++++			
17		4-[7-Bromo-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	478.0, 2.07	++++	++++			

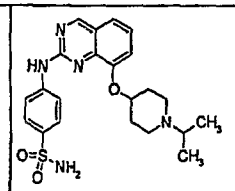
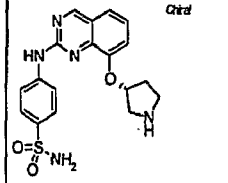
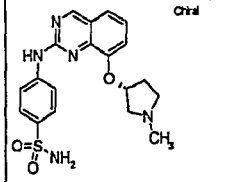
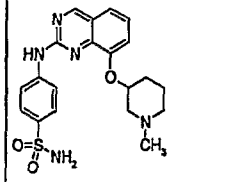
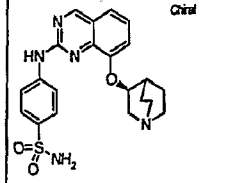
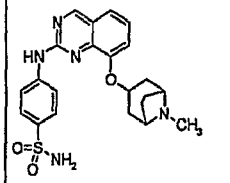
WO 2007/117607 PCT/US2007/008592

18		4-[8-(Piperidin-4-yloxy)-7-pyridin-3-yl-quinazolin-2-ylamino]-benzenesulfonamide	477.1, 1.70	++++	++++			+++
19		4-[8-(Piperidin-4-yloxy)-2-(4-sulfamoyl-phenylamino)-quinazolin-7-yl]-benzamide	519.1, 1.98	++++	+++			
20		4-[8-(Piperidin-4-yloxy)-7-pyridin-4-yl-quinazolin-2-ylamino]-benzenesulfonamide	477.1, 1.69	++++	++++			
21		4-[7-(6-Amino-pyridin-3-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	492.1, 1.75	++++	++++			+++
22		4-[7-(2-Amino-pyrimidin-5-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	493.1, 1.80	++++	+++			
23		4-[7-(5-Methoxy-pyridin-3-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	507.1, 1.83	++++	++++			+++

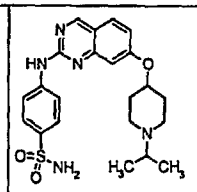
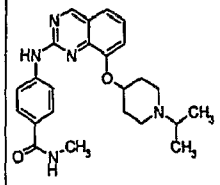
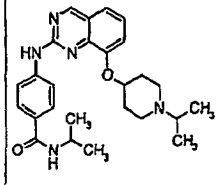
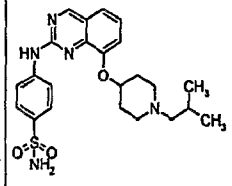
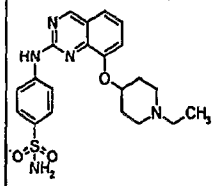
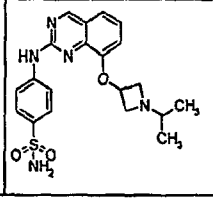
WO 2007/117607 PCT/US2007/008592

24		4-[8-(Piperidin-4-yloxy)-7-(1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	466.1, 1.88	++++	++++			+++
25		4-[7-(1-Methyl-1H-pyrazol-4-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	480.1, 1.97	++++	++++			+++
26		4-[7-Oxazol-2-yl-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	467.1, 1.94	++++	++++			+++
27		4-[8-(Piperidin-4-yloxy)-7-thiazol-2-yl-quinazolin-2-ylamino]-benzenesulfonamide	483.1, 2.08	++++	++++			++++
28		4-[8-(Piperidin-4-yloxy)-7-pyridin-2-yl-quinazolin-2-ylamino]-benzenesulfonamide	477.1, 1.73	++++	++++			+++
29		4-[7-Cyano-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	425.1, 1.95	++++	++++			

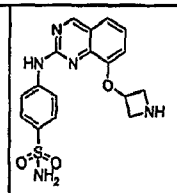
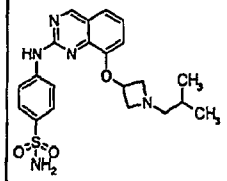
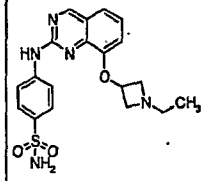
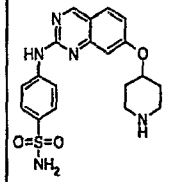
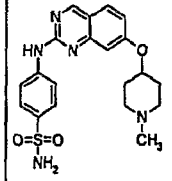
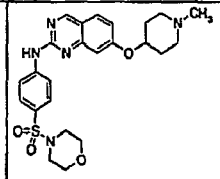
30		4-[8-(Piperidin-4-yloxy)-quinazolin-2-ylamino]-benzamide	364.1, 1.81	++++	++++			
31		4-[8-(Piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	400.1, 1.91	++++	++++	++++		++++
32		4-[8-((S)-Pyrrolidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	386.1, 1.88	++++	++++			
33		4-[8-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	426.1, 2.11	++++	++++			
34		4-[8-((S)-1-Methyl-pyrrolidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	400.1, 1.89	++++	++++			
35		4-[8-(1-Methyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	414.2, 1.95	++++	++++			++++

36		4-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	442.1, 2.11	++++	++++	++++		++++
37		4-[8-((R)-Pyrrolidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	386.1, 1.85	++++	++++			+++
38		4-[8-((R)-1-Methyl-pyrrolidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	400.1, 1.86	++++	++++			
39		4-[8-(1-Methyl-piperidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	414.1, 1.97	++++	++++			
40		4-[8-((S)-3-quinuclidinyloxy)-quinazolin-2-ylamino]-benzenesulfonamide	426.1, 1.72	++++	++++	++++		++++
41		4-[8-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	440.1, 2.05	++++	++++	++++		++++

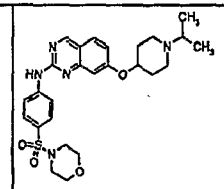
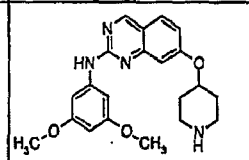
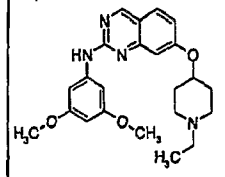
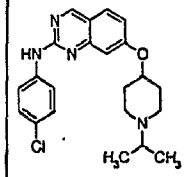
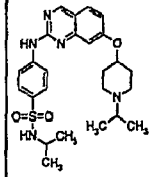
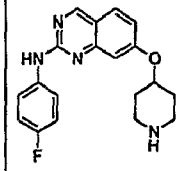
WO 2007/117607 PCT/US2007/008592

42		4-[7-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	442.0, 2.02	++++	++++	++++		++++
43		4-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-N-methyl-benzamide	420.1, 2.13	++++	++++			++++
44		N-Isopropyl-4-[8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzamide	448.1, 2.42	++++	++++	++++		++++
45		4-[8-(1-Isobutyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	456.2, 2.25	++++	++++	++++		++++
46		4-[8-(1-Ethyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	428.1, 2.05	++++	++++			+++
47		4-[8-(1-Isopropyl-azetidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	414.1, 1.93	++++	++++			

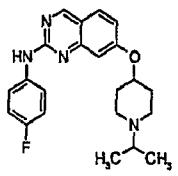
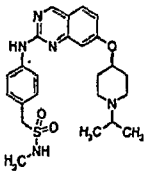
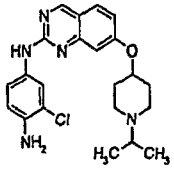
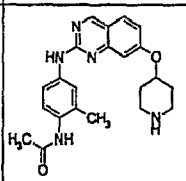
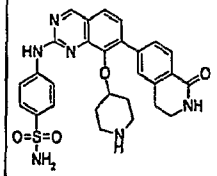
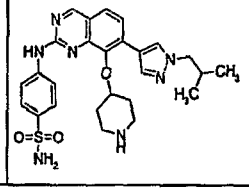
WO 2007/117607 PCT/US2007/008592

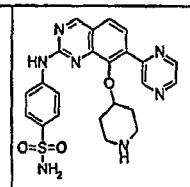
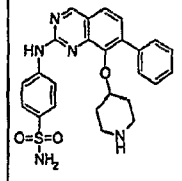
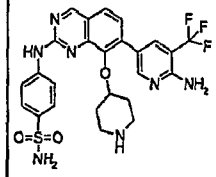
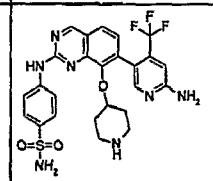
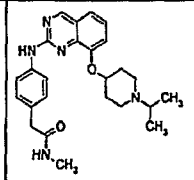
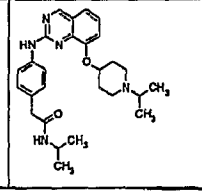
48		4-[8-(Azetidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	372.1, 1.76	++++	+++			
49		4-[8-(1-Isobutyl-azetidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	428.1, 2.14	++++	++++			
50		4-[8-(1-Ethyl-azetidin-3-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	400.1, 1.91	++++	++++			
51		4-[7-(Piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	400.1, 1.813	++++	++++	++++		++++
52		4-[7-(1-Methyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	414.1, 1.803	++++	++++	++++	++++	++++
53		[7-(1-Methyl-piperidin-4-yloxy)-quinazolin-2-yl]-[4-(morpholine-4-sulfonyl)-phenyl]-amine	484.1, 2.07	++++	++++	++++		++++

WO 2007/117607 PCT/US2007/008592

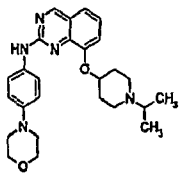
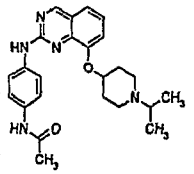
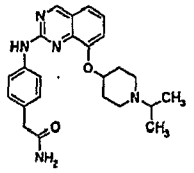
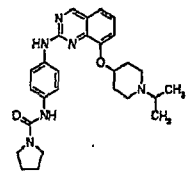
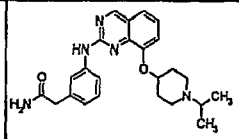
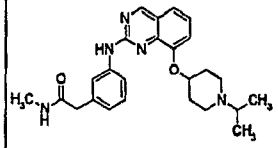
54		[7-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-[4-(morpholine-4-sulfonyl)-phenyl]-amine	512.1, 2.18	++++	++++	++++		
55		(3,5-Dimethoxy-phenyl)-[7-(piperidin-4-yloxy)-quinazolin-2-yl]-amine	381.1, 2.19	++++		++++		++++
56		(3,5-Dimethoxy-phenyl)-[7-(1-ethyl-piperidin-4-yloxy)-quinazolin-2-yl]-amine	409.4, 2.39	++++		++++		
57		(4-Chloro-phenyl)-[7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-amine	397.1, 2.53	++++		++++		
58		N-Isopropyl-4-[7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	484.2, 2.19	++++		++++		++++
59		(4-Fluoro-phenyl)-[7-(piperidin-4-yloxy)-quinazolin-2-yl]-amine	339.0, 1.92	++++		++++		++++

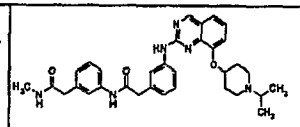
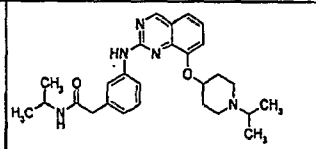
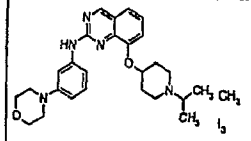
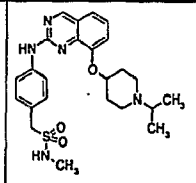
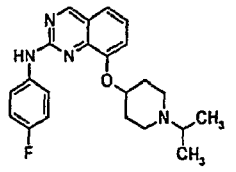
WO 2007/117607 PCT/US2007/008592

60		(4-Fluoro-phenyl)-[7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-amine	381.1, 2.07	++++		+++		
61		C-{4-[7-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide	470.1, 1.84	++++		++++		++++
62		2-Chloro-N*4*-[7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-benzene-1,4-diamine	412.1, 1.86	++++		+++		
63		N-{2-Methyl-4-[7-(piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	392.2, 1.70	++++		++++		++++
64		4-[7-(1-Oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	545.1, 2.07	++++	+++			
65		4-[7-(1-Isobutyl-1H-pyrazol-4-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	522.1, 2.27	++++	++++			+++

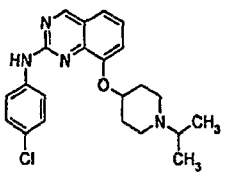
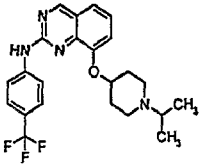
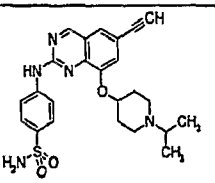
66		4-[8-(Piperidin-4-yloxy)-7-pyrazin-2-yl-quinazolin-2-ylamino]-benzenesulfonamide	478.0, 1.91	++++	++++			+++
67		4-[7-Phenyl-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	476.1, 2.28	++++	++++	++++		++++
68		4-[7-(6-Amino-5-trifluoromethyl-pyridin-3-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	560.1, 2.11	++++		++++		+++
69		4-[7-(6-Amino-4-trifluoromethyl-pyridin-3-yl)-8-(piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	560.1, 1.99	++++		+++		
70		2-{4-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-N-methyl-acetamide	434.1, 1.85	++++		++++		++
71		N-Isopropyl-2-{4-[8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	462.2, 2.09	++++		++++		+++

WO 2007/117607 PCT/US2007/008592

72		[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-(4-morpholin-4-yl-phenyl)-amine	448.2, 1.92	++++		++++		++++
73		N-{4-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	420.1, 1.90	++++		++++		+++
74		2-{4-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	420.1, 1.79	++++		++++		
75		Pyrrolidine-1-carboxylic acid {4-[8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-amide	475.2, 2.15	++++		++++		
76		2-{3-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	420.1, 1.83	++++		++++		
77		2-{3-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-N-methyl-acetamide	434.2, 1.87	++++		++++		++++

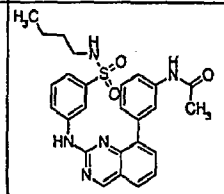
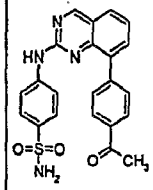
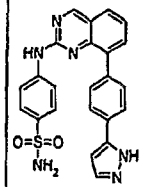
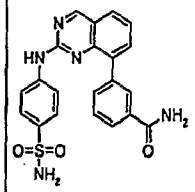
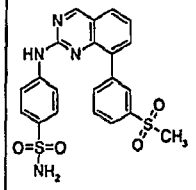
78		2-{3-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-N-(3-methylcarbamoylmethyl-phenyl)-acetamide	567.2, 2.05	++++		++++		
79		N-Isopropyl-2-{3-[8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	462.2, 2.05	++++		++++		
80		[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-(3-morpholin-4-yl-phenyl)-amine	448.2, 2.01	++++		+++		
81		N-{3-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-acetamide	420.2, 1.90	++++		++++		++++
82		C-{4-[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide	470.1, 2.00	++++		++++		
83		(4-Fluoro-phenyl)-[8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-amine	381.1, 2.17	++++		+++		

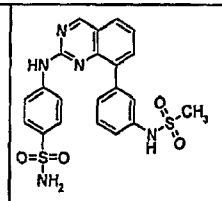
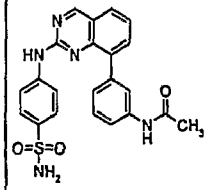
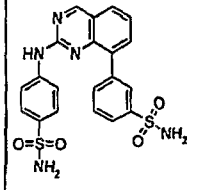
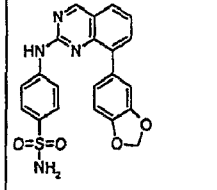
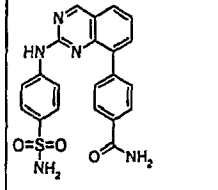
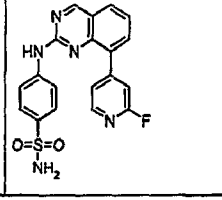
WO 2007/117607 PCT/US2007/008592

84		(4-Chloro-phenyl)-[8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-amine	397.1, 2.37	++++		++++		
85		[8-(1-Isopropyl-piperidin-4-yloxy)-quinazolin-2-yl]-(4-trifluoromethyl-phenyl)-amine	431.1, 3.09	++++		++++		
86		4-[6-Ethynyl-8-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-ylamino]-benzenesulfonamide	466, 2.87	++++		++++		++++

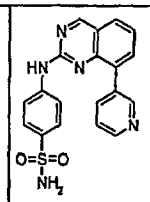
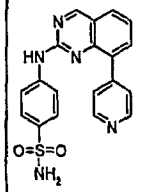
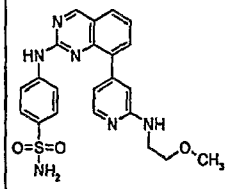
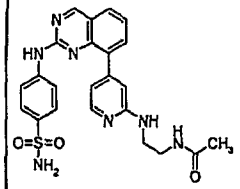
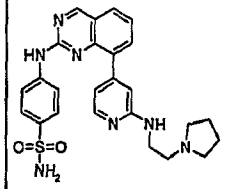
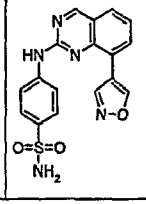
WO 2007/117607 PCT/US2007/008592

Table 2

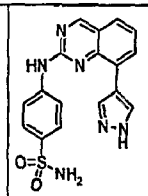
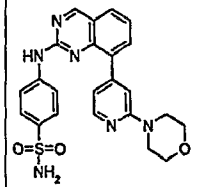
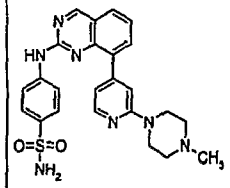
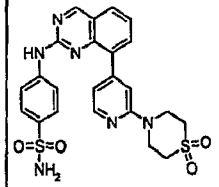
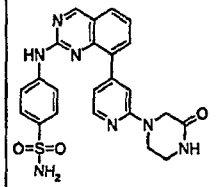
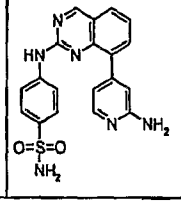
Compound	Structure	Name	LC/MS (M+1(m/z), Rt(min))	PDK1 IC_{50}	CP EC_{50} A2780	CP EC_{50} PC3	CP EC_{50} PC3MM	PAKT308 PC3 IC_{50}
87		N-{3-[2-(3-Butylsulfamoyl-phenylamino)-quinazolin-8-yl]-phenyl}-acetamide	489.6 (FW)	+++				
88		4-[8-(4-Acetyl-phenyl)-quinazolin-2-ylamino]-benzenesulfonamide	419.0, 2.69	++++	+++			
89		4-{8-[4-(2H-Pyrazol-3-yl)-phenyl]-quinazolin-2-ylamino}-benzenesulfonamide	443.2, 2.33	++++	++++			
90		3-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-benzamide	420.0, 2.25	++++	++++			
91		4-[8-(3-Methanesulfonyl-phenyl)-quinazolin-2-ylamino]-benzenesulfonamide	455.0, 2.45	++++	++++			

92		4-[8-(3-Methanesulfonylamino-phenyl)-quinazolin-2-ylamino]-benzenesulfonamide	470.0, 2.47	++++	++++			
93		N-{3-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-phenyl}-acetamide	434.0, 2.39	++++	++++			
94		N-{3-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-phenyl}-sulfonamide	456.0, 2.30	++++	++++			
95		4-(8-Benzo[1,3]dioxol-5-yl-quinazolin-2-ylamino)-benzenesulfonamide	421.0, 2.78	++++	++++			
96		4-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-benzamide	420.1, 2.28	++++	+++			
97		4-[8-(2-Fluoro-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	396.0, 2.55	++++	++++			

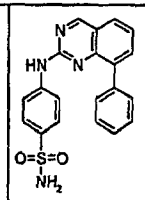
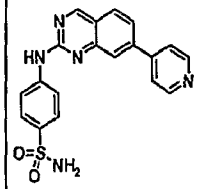
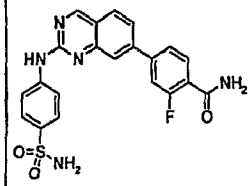
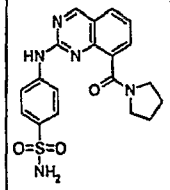
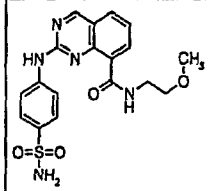
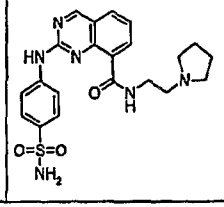
WO 2007/117607 PCT/US2007/008592

98		4-(8-Pyridin-3-yl-quinazolin-2-ylamino)-benzenesulfonamide	378.0, 1.84	++++	+++			
99		4-(8-Pyridin-4-yl-quinazolin-2-ylamino)-benzenesulfonamide	378.0, 1.83	++++	+++			
100		4-{8-[2-(2-Methoxy-ethylamino)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	451.0, 2.01	++++	++++			
101		N-(2-{4-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-pyridin-2-ylamino}-ethyl)-acetamide	478.0, 1.89	++++	++++			
102		4-{8-[2-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.79	++++	++++			
103		4-(8-Isoxazol-4-yl-quinazolin-2-ylamino)-benzenesulfonamide	368.0, 2.40	++++	++++			

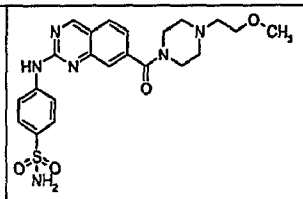
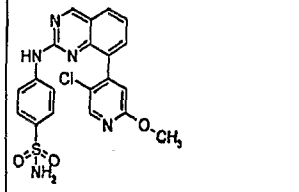
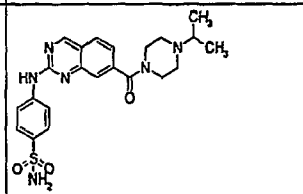
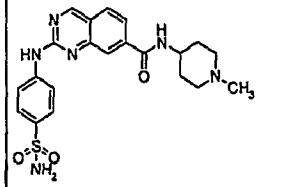
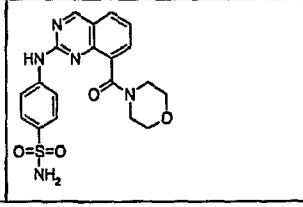
WO 2007/117607 PCT/US2007/008592

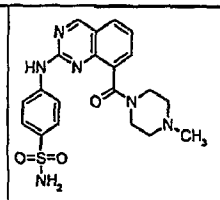
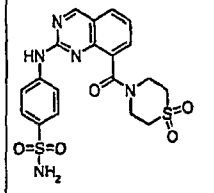
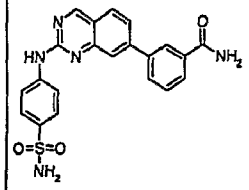
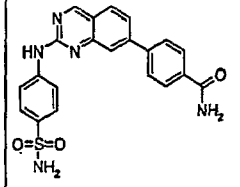
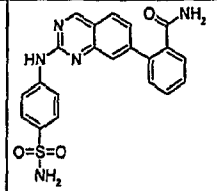
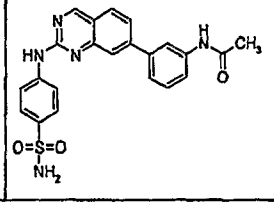
104		4-[8-(1H-Pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	367.1, 2.13	++++	++++			
105		4-[8-(2-Morpholin-4-yl-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	463.0, 1.98	++++	+++			
106		4-{8-[2-(4-Methyl-piperazin-1-yl)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	476.1, 1.79	++++	++++			
107		4-{8-[2-(1,1-Dioxo-1lambda*6*-thiomorpholin-4-yl)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	511.0, 1.99	++++	++++			
108		4-{8-[2-(3-Oxo-piperazin-1-yl)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	476.0, 1.84	++++	++++			
109		4-[8-(2-Amino-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	393.1, 1.89	++++	+++			

WO 2007/117607 PCT/US2007/008592

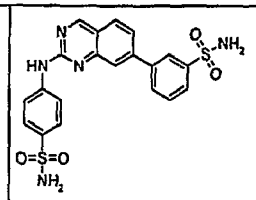
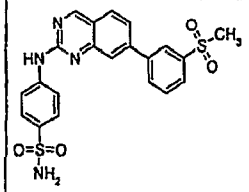
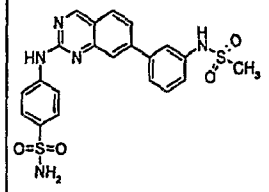
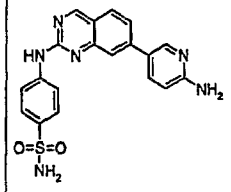
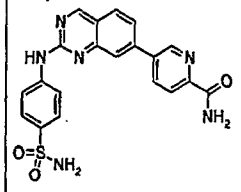
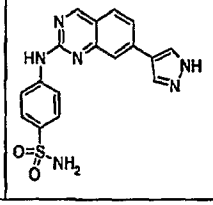
110		4-(8-Phenyl-quinazolin-2-ylamino)-benzenesulfonamide	377.0, 2.84	++++	++++			
111		4-(7-Pyridin-4-yl-quinazolin-2-ylamino)-benzenesulfonamide	378.1, 1.65					
112		2-Fluoro-4-[2-(4-sulfamoyl-phenylamino)-quinazolin-7-yl]-benzamide	438.0, 2.19	++++	+++			
113		4-[8-(Pyrrolidine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	398.0, 2.06	++++	+++			
114		2-(4-Sulfamoyl-phenylamino)-quinazoline-8-carboxylic acid (2-methoxy-ethyl)-amide	402.0, 2.09	+++	++++			
115		2-(4-Sulfamoyl-phenylamino)-quinazoline-8-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide	441.0, 1.84	+++	++++			

WO 2007/117607 PCT/US2007/008592

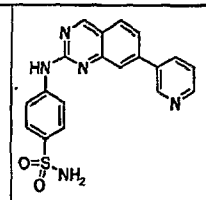
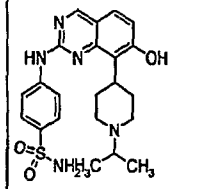
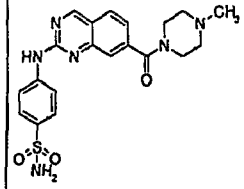
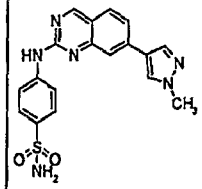
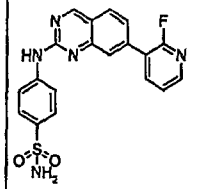
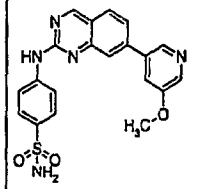
116		4-{7-[4-(2-Methoxy-ethyl)-piperazine-1-carbonyl]-quinazolin-2-ylamino}-benzenesulfonamide	471.0, 1.67	++	+++			
117		4-[8-(5-Chloro-2-methoxy-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	442.0, 3.70	++++	++++			
118		4-[7-(4-Isopropyl-piperazine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	455.1, 1.71	++	+++			
119		2-(4-Sulfamoyl-phenylamino)-quinazoline-7-carboxylic acid (1-methyl-piperidin-4-yl)-amide	441.1, 1.74	++++	+++			
120		4-[8-(Morpholine-4-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	414.0, 1.92	+++	+++			

121		4-[8-(4-Methyl-piperazine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	427.1, 1.59	++++	+++			
122		4-[8-(1,1-Dioxo-1lambda*6*-thiomorpholine-4-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	462.0, 1.83	++	+++			
123		3-[2-(4-Sulfamoyl-phenylamino)-quinazolin-7-yl]-benzamide	419.9, 2.569	++++	+++			
124		4-[2-(4-Sulfamoyl-phenylamino)-quinazolin-7-yl]-benzamide	420.1, 3.24	++++	+++			
125		2-[2-(4-Sulfamoyl-phenylamino)-quinazolin-7-yl]-benzamide	420.0, 2.404	++++				
126		N-{3-[2-(4-Sulfamoyl-phenylamino)-quinazolin-7-yl]-phenyl}-acetamide	434.0, 2.882	+++				

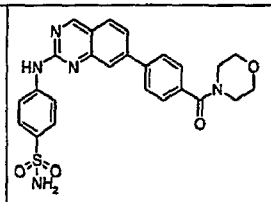
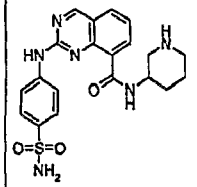
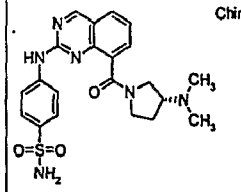
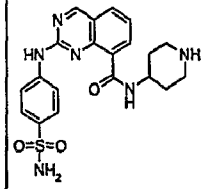
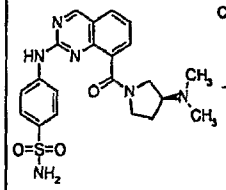
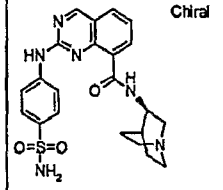
WO 2007/117607 PCT/US2007/008592

127		N-{3-[2-(4-Sulfamoyl-phenylamino)-quinazolin-7-yl]-phenyl}-sulfonamide	456.0, 2.766	++++	+++			
128		4-[7-(3-Methanesulfonyl-phenyl)-quinazolin-2-ylamino]-benzenesulfonamide	454.9, 3.039	++++				
129		4-[7-(3-Methanesulfonylamino-phenyl)-quinazolin-2-ylamino]-benzenesulfonamide	469.9, 3.91	++				
130		4-[7-(6-Amino-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	393.0, 1.948	++++	++++			
131		5-[2-(4-Sulfamoyl-phenylamino)-quinazolin-7-yl]-pyridine-2-carboxylic acid amide	421.0, 2.10	++++	+++			
132		4-[7-(1H-Pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	367.0, 1.92	++++	++++			

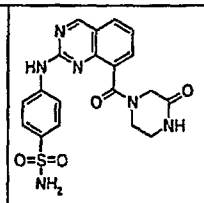
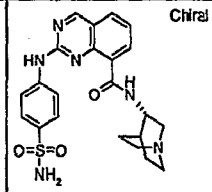
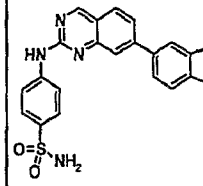
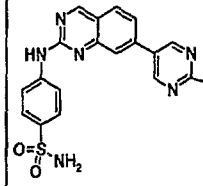
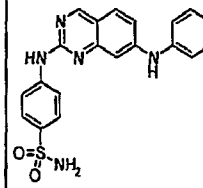
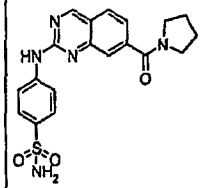
WO 2007/117607 PCT/US2007/008592

133		4-(7-Pyridin-3-yl-quinazolin-2-ylamino)-benzenesulfonamide	378.0, 1.73	++++	++++			++++
134		4-[7-Hydroxy-8-(1-isopropyl-piperidin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	442.0, 1.94	++++	++++	++++		++++
135		4-[7-(4-Methyl-piperazine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	427.1, 1.52	++	+++			
136		4-[7-(1-Methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	381.0, 2.49	++++	++++	++++		++++
137		4-[7-(2-Fluoro-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	396.0, 3.07	++++	++++	++++		++++
138		4-[7-(5-Methoxy-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	408.0, 2.12	++++	++++			+++

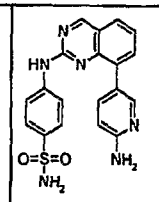
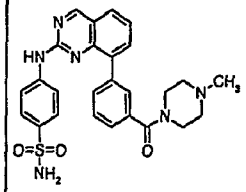
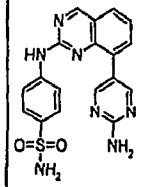
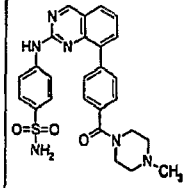
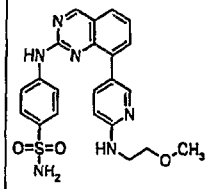
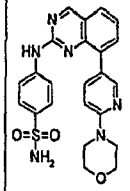
WO 2007/117607 PCT/US2007/008592

139		4-{7-[4-(Morpholine-4-carbonyl)-phenyl]-quinazolin-2-ylamino}-benzenesulfonamide	490.0, 2.84	++++	+++			
140		2-(4-Sulfamoyl-phenylamino)-quinazoline-8-carboxylic acid piperidin-3-ylamide	427.1, 1.83	++++	+++			
141	 Chiral	4-[8-((R)-3-Dimethylamino-pyrrolidine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	441.0, 1.59	++++	+++			
142		2-(4-Sulfamoyl-phenylamino)-quinazoline-8-carboxylic acid piperidin-4-ylamide	427.1, 1.78	++++	+++			
143	 Chiral	4-[8-((S)-3-Dimethylamino-pyrrolidine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	441.1, 1.59	++++	+++			
144	 Chiral	2-(4-Sulfamoyl-phenylamino)-quinazoline-8-carboxylic acid (R)-3-quinuclidinylamide	453.1, 1.80	+++	+++			

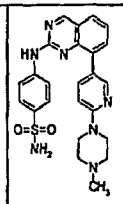
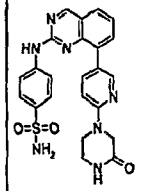
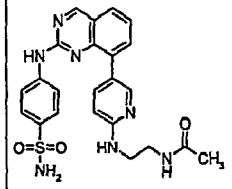
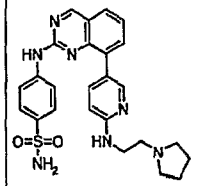
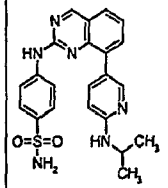
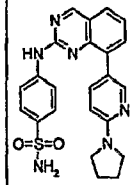
WO 2007/117607 PCT/US2007/008592

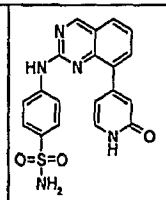
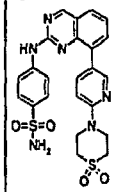
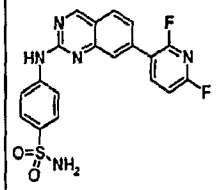
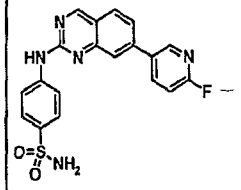
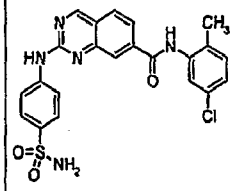
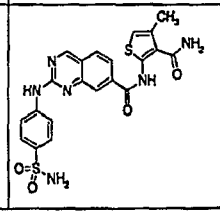
145		4-[8-(3-Oxo-piperazine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	427.0, 1.66					
146	 Chiral	2-(4-Sulfamoyl-phenylamino)-quinazoline-8-carboxylic acid (S)-3-quinuclidinylamide	453.1, 1.80					
147		4-[7-(1H-Indazol-6-yl)-quinazolin-2-ylamino]-benzenesulfonamide	417.0, 2.38					
148		4-[7-(2-Methoxy-pyrimidin-5-yl)-quinazolin-2-ylamino]-benzenesulfonamide	409.0, 2.29					
149		4-[7-(1H-Indazol-6-ylamino)-quinazolin-2-ylamino]-benzenesulfonamide	432.0, 2.088					
150		4-[7-(Pyrrolidine-1-carbonyl)-quinazolin-2-ylamino]-benzenesulfonamide	398.1, 2.44					

WO 2007/117607 PCT/US2007/008592

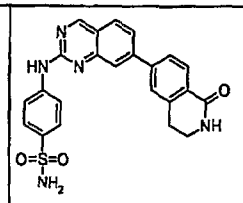
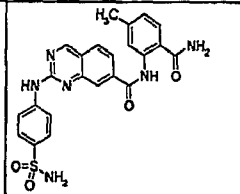
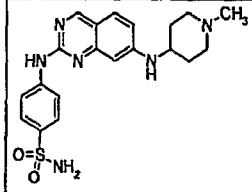
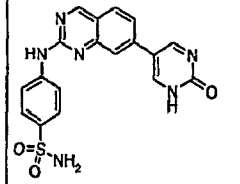
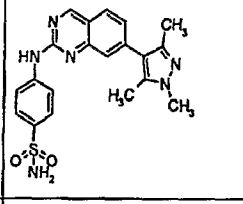
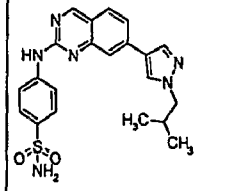
151		4-[8-(6-Amino-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	393.0, 1.93					
152		4-{8-[3-(4-Methyl-piperazine-1-carbonyl)-phenyl]-quinazolin-2-ylamino}-benzenesulfonamide	503.0, 2.07					
153		4-[8-(2-Amino-pyrimidin-5-yl)-quinazolin-2-ylamino]-benzenesulfonamide	394.0, 1.90					
154		4-{8-[4-(4-Methyl-piperazine-1-carbonyl)-phenyl]-quinazolin-2-ylamino}-benzenesulfonamide	503.1, 2.08					
155		4-{8-[6-(2-Methoxy-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	451.0, 2.03					
156		4-[8-(6-Morpholin-4-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	463.1, 1.99					

WO 2007/117607 PCT/US2007/008592

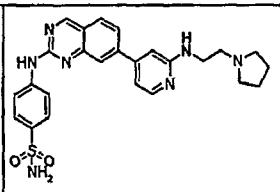
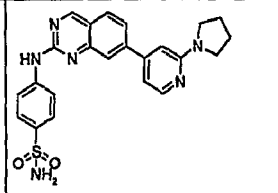
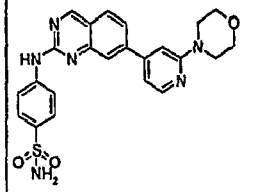
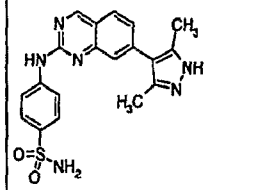
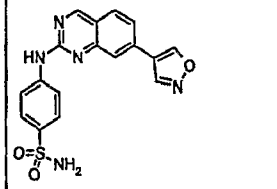
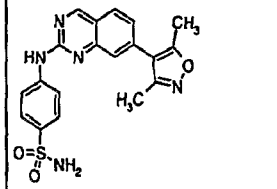
157		4-{8-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	476.1, 1.86					
158		4-{8-[6-(3-Oxo-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	476.1, 1.89					
159		N-(2-{5-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-pyridin-2-ylamino}-ethyl)-acetamide	478.1, 1.93					
160		4-{8-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.82					
161		4-[8-(6-Isopropylamino-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	435.1, 2.10					
162		4-[8-(6-Pyrrolidin-1-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	447.1, 2.14					

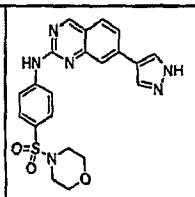
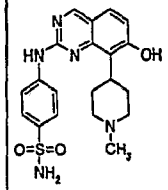
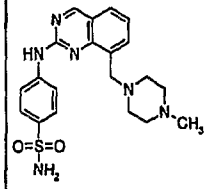
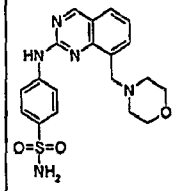
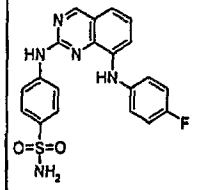
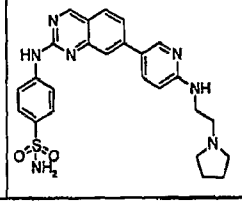
163		4-[8-(2-Oxo-1,2-dihydro-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	394.0, 2.02					
164		4-{8-[6-(1,1-Dioxo-1lambda*6*-thiomorpholin-4-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	511.0, 2.11					
165		4-[7-(2,6-Difluoro-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	414.0, 2.68					
166		4-[7-(6-Fluoro-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	396.0, 2.47					
167		2-(4-Sulfamoyl-phenylamino)-quinazoline-7-carboxylic acid (5-chloro-2-methyl-phenyl)-amide	468.0, 2.73					
168		2-(4-Sulfamoyl-phenylamino)-quinazoline-7-carboxylic acid (3-carbamoyl-4-methyl-thiophen-2-yl)-amide	483.0, 2.47					

WO 2007/117607 PCT/US2007/008592

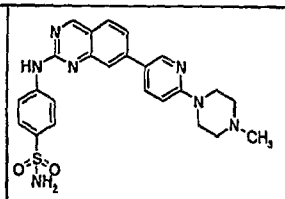
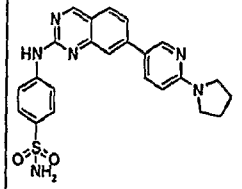
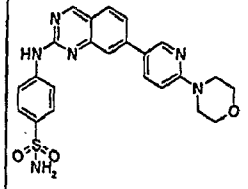
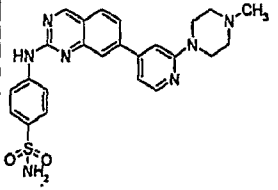
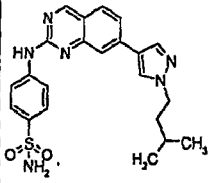
169		4-[7-(1-Oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)-quinazolin-2-ylamino]-benzenesulfonamide	446.0, 2.734					
170		2-(4-Sulfamoyl-phenylamino)-quinazoline-7-carboxylic acid (2-carbamoyl-5-methyl-phenyl)-amide	477.0, 2.49					
171		4-[7-(1-Methyl-piperidin-4-ylamino)-quinazolin-2-ylamino]-benzenesulfonamide	413.1, 1.59					
172		4-[7-(2-Oxo-1,2-dihydro-pyrimidin-5-yl)-quinazolin-2-ylamino]-benzenesulfonamide	395.0, 1.71					
173		4-[7-(1,3,5-Trimethyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	409.1, 2.48					
174		4-[7-(1-Isobutyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	423.1, 3.30					

WO 2007/117607 PCT/US2007/008592

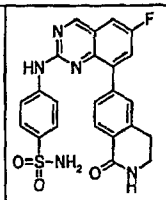
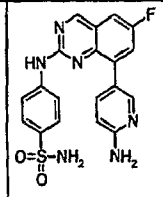
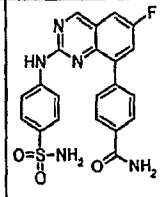
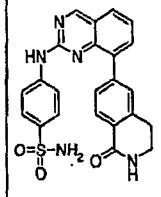
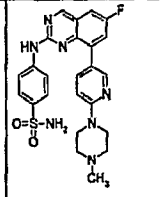
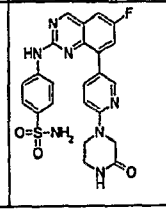
175		4-{7-[2-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.79					
176		4-[7-(2-Pyrrolidin-1-yl-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	447.1, 2.29					
177		4-[7-(2-Morpholin-4-yl-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	463.1, 2.101					
178		4-[7-(3,5-Dimethyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	395.0, 1.94					
179		4-(7-Isoxazol-4-yl-quinazolin-2-ylamino)-benzenesulfonamide	368.0, 2.10					
180		4-[7-(3,5-Dimethyl-isoxazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	396.0, 2.40					

181		[4-(Morpholine-4-sulfonyl)-phenyl]-[7-(1H-pyrazol-4-yl)-quinazolin-2-yl]-amine	437.1, 2.34					
182		4-[7-Hydroxy-8-(1-methyl-piperidin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	414.1, 2.01					
183		4-[8-(4-Methyl-piperazin-1-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	413.1, 1.60					
184		4-(8-Morpholin-4-ylmethyl-quinazolin-2-ylamino)-benzenesulfonamide	400.1, 1.71					
185		4-[8-(4-Fluoro-phenylamino)-quinazolin-2-ylamino]-benzenesulfonamide	410.1, 2.93					
186		4-{7-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.78					

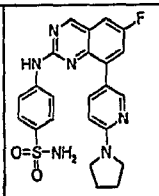
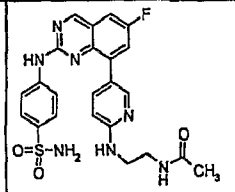
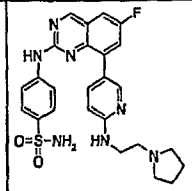
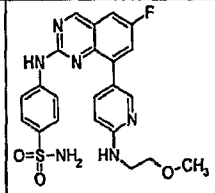
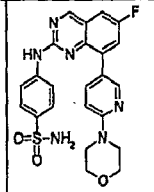
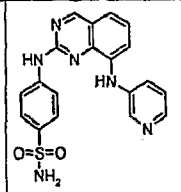
WO 2007/117607 PCT/US2007/008592

187		4-{7-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	476.1, 1.86					
188		4-[7-(6-Pyrrolidin-1-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	447.1, 2.22					
189		4-[7-(6-Morpholin-4-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	463.1, 2.11					
190		4-{7-[2-(4-Methyl-piperazin-1-yl)-pyridin-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	476.1, 1.85					
191		4-{7-[1-(3-Methyl-butyl)-1H-pyrazol-4-yl]-quinazolin-2-ylamino}-benzenesulfonamide	437.1, 3.61					

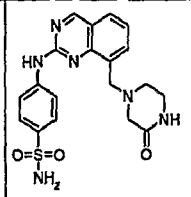
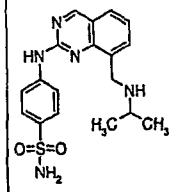
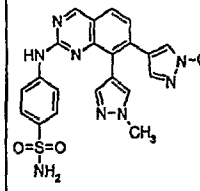
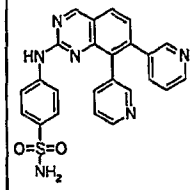
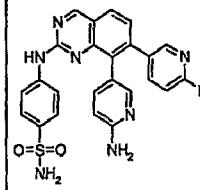
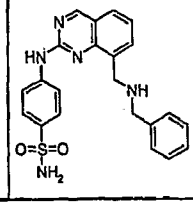
WO 2007/117607 PCT/US2007/008592

192		4-[6-Fluoro-8-(1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)-quinazolin-2-ylamino]-benzenesulfonamide	464.0, 3.047					
193		4-[8-(6-Amino-pyridin-3-yl)-6-fluoro-quinazolin-2-ylamino]-benzenesulfonamide	411.0, 2.173					
194		4-[6-Fluoro-2-(4-sulfamoyl-phenylamino)-quinazolin-8-yl]-benzamide	438.0, 2.961					
195		4-[8-(1-Oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)-quinazolin-2-ylamino]-benzenesulfonamide	446.0, 2.935					
196		4-{6-Fluoro-8-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	494.0, 2.107					
197		4-{6-Fluoro-8-[6-(3-oxo-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	494.0, 2.131					

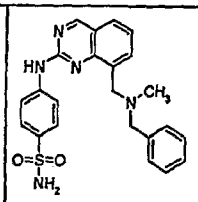
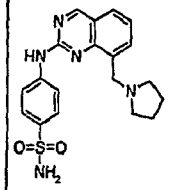
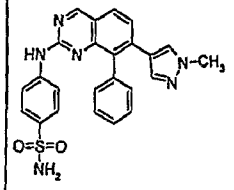
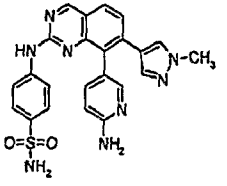
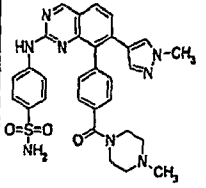
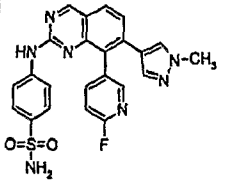
WO 2007/117607 PCT/US2007/008592

198		4-[6-Fluoro-8-(6-pyrrolidin-1-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	465.0, 2.434					
199		N-(2-{5-[6-Fluoro-2-(4-sulfamoyl-phenylamino)-quinazolin-8-yl]-pyridin-2-ylamino}-ethyl)-acetamide	496.0, 2.434					
200		4-{6-Fluoro-8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	508.1, 1.959					
201		4-{6-Fluoro-8-[6-(2-methoxy-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	469.0, 2.319					
202		4-[6-Fluoro-8-(6-morpholin-4-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	481.0, 2.328					
203		4-[8-(Pyridin-3-ylamino)-quinazolin-2-ylamino]-benzenesulfonamide	393.0, 1.83					

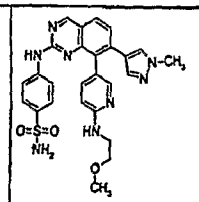
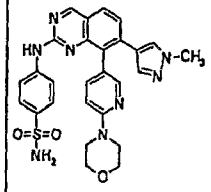
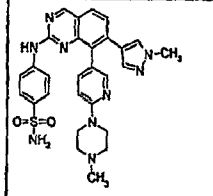
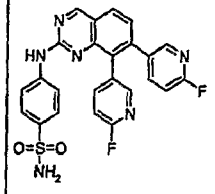
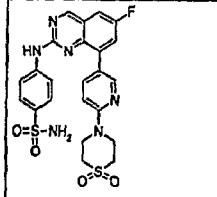
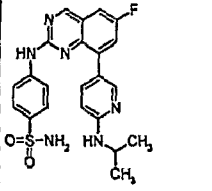
WO 2007/117607 PCT/US2007/008592

204		4-[8-(3-Oxo-piperazin-1-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	413.0, 1.65					
205		4-[8-(Isopropylamino-methyl)-quinazolin-2-ylamino]-benzenesulfonamide	372.0, 1.82					
206		4-[7,8-Bis-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	461.0, 2.13					
207		4-(7,8-Di-pyridin-3-yl-quinazolin-2-ylamino)-benzenesulfonamide	455.0, 1.63					
208		4-[7,8-Bis-(6-amino-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	485.0, 1.69					
209		4-[8-(Benzylamino-methyl)-quinazolin-2-ylamino]-benzenesulfonamide	420.1, 2.06					

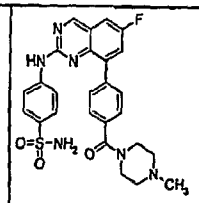
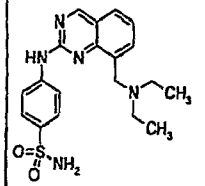
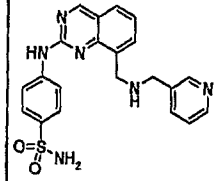
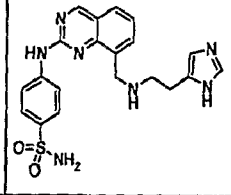
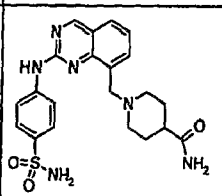
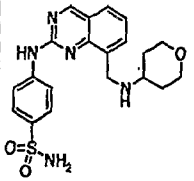
WO 2007/117607 PCT/US2007/008592

210		4-{8-[(Benzyl-methyl-amino)-methyl]-quinazolin-2-ylamino}-benzenesulfonamide	434.0, 2.07					
211		4-(8-Pyrrolidin-1-ylmethyl-quinazolin-2-ylamino)-benzenesulfonamide	384.1, 1.85					
212		4-[7-(1-Methyl-1H-pyrazol-4-yl)-8-phenyl-quinazolin-2-ylamino]-benzenesulfonamide	457.0, 2.52					
213		4-[8-(6-Amino-pyridin-3-yl)-7-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	473.1, 1.94					
214		4-[8-[4-(4-Methyl-piperazine-1-carbonyl)-phenyl]-7-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamid□e	583.1, 2.06					
215		4-[8-(6-Fluoro-pyridin-3-yl)-7-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	476.0, 2.33					

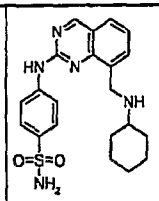
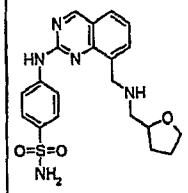
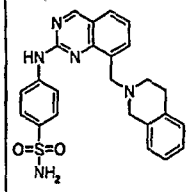
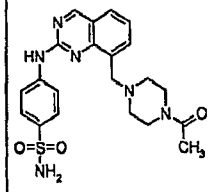
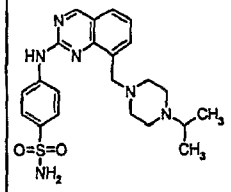
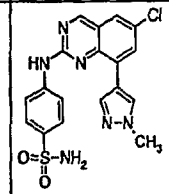
WO 2007/117607 PCT/US2007/008592

216		4-[8-[6-(2-Methoxy-ethylamino)-pyridin-3-yl]-7-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	531.1, 2.02					
217		4-[7-(1-Methyl-1H-pyrazol-4-yl)-8-(6-morpholin-4-yl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	543.0, 2.00					
218		4-[8-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-yl]-7-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	556.1, 1.92					
219		4-[7,8-Bis-(6-fluoro-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	491.0, 2.60					
220		4-{8-[6-(1,1-Dioxo-1lambda*6*-thiomorpholin-4-yl)-pyridin-3-yl]-6-fluoro-quinazolin-2-ylamino}-benzenesulfonamide	528.9, 2.730					
221		4-[6-Fluoro-8-(6-isopropylamino-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	453.0, 2.468					

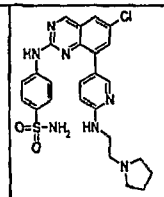
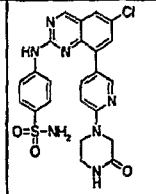
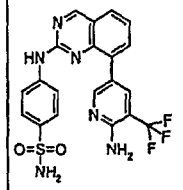
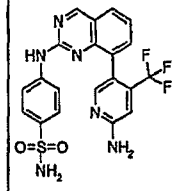
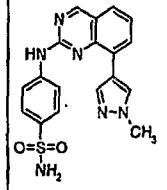
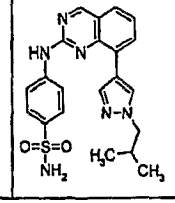
WO 2007/117607 PCT/US2007/008592

222		4-{6-Fluoro-8-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-quinazolin-2-ylamino}-benzenesulfonamide	521.0, 2.43					
223		4-(8-Diethylaminomethyl-quinazolin-2-ylamino)-benzenesulfonamide	386.0, 1.82					
224		4-(8-{[(Pyridin-3-ylmethyl)-amino]-methyl}-quinazolin-2-ylamino)-benzenesulfonamide	421.0, 1.61					
225		4-(8-{[2-(3H-Imidazol-4-yl)-ethylamino]-methyl}-quinazolin-2-ylamino)-benzenesulfonamide	424.0, 1.60					
226		1-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-ylmethyl]-piperidine-4-carboxylic acid amide	441.0, 1.68					
227		4-{8-[(Tetrahydro-pyran-4-ylamino)-methyl]-quinazolin-2-ylamino}-benzenesulfonamide	414.1, 1.75					

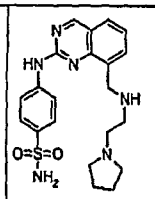
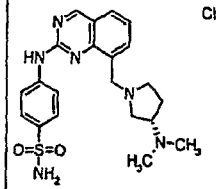
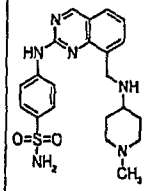
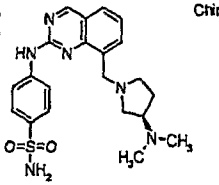
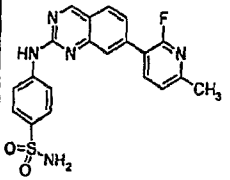
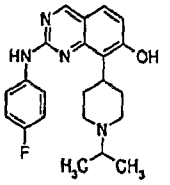
WO 2007/117607 PCT/US2007/008592

228		4-(8-Cyclohexylaminomethyl-quinazolin-2-ylamino)-benzenesulfonamide	412.1, 2.01					
229		4-(8-{[(Tetrahydro-furan-2-ylmethyl)-amino]-methyl}-quinazolin-2-ylamino)-benzenesulfonamide	414.2, 1.92					
230		4-[8-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	446.2, 2.13					
231		4-[8-(4-Acetyl-piperazin-1-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	441.2, 1.60					
232		4-[8-(4-Isopropyl-piperazin-1-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	441.2, 1.53					
233		4-[6-Chloro-8-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	414.9, 3.386					

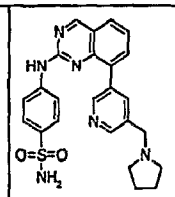
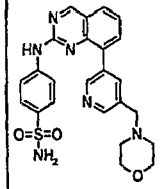
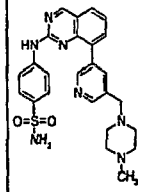
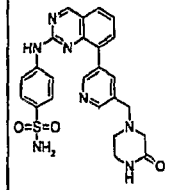
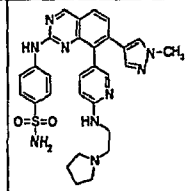
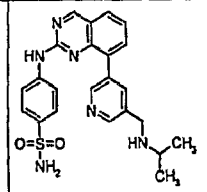
WO 2007/117607 PCT/US2007/008592

234		4-{6-Chloro-8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	524.1, 2.174					
235		4-{6-Chloro-8-[6-(3-oxo-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	510.0, 2.343					
236		4-[8-(6-Amino-5-trifluoromethyl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	461.1, 2.24					
237		4-[8-(6-Amino-4-trifluoromethyl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	461.1, 2.15					
238		4-[8-(1-Methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	381.0, 2.28					
239		4-[8-(1-Isobutyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	423.1, 2.71					

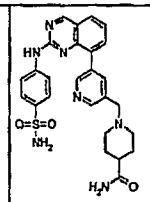
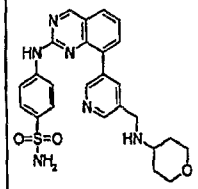
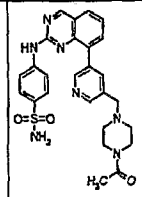
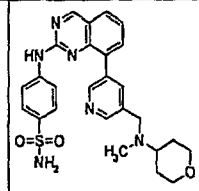
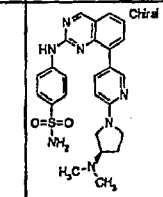
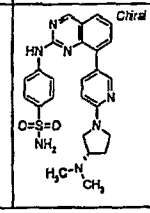
WO 2007/117607 PCT/US2007/008592

240		4-{8-[(2-Pyrrolidin-1-yl-ethylamino)-methyl]-quinazolin-2-ylamino}-benzenesulfonamide	427.1, 1.65					
241	 Chiral	4-[8-((S)-3-Dimethylamino-pyrrolidin-1-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	427.1, 1.64					
242		4-{8-[(1-Methyl-piperidin-4-ylamino)-methyl]-quinazolin-2-ylamino}-benzenesulfonamide	427.1, 1.60					
243	 Chiral	4-[8-((R)-3-Dimethylamino-pyrrolidin-1-ylmethyl)-quinazolin-2-ylamino]-benzenesulfonamide	427.1, 1.64					
244		4-[7-(2-Fluoro-6-methyl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	410.0, 2.56					
245		2-(4-Fluoro-phenylamino)-8-(1-isopropyl-piperidin-4-yl)-quinazolin-7-ol	381.1, 2.42					

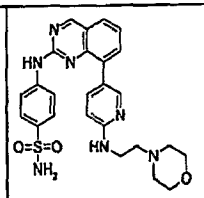
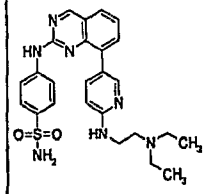
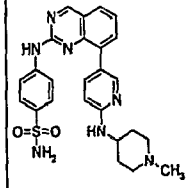
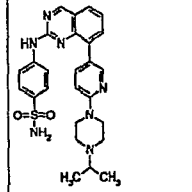
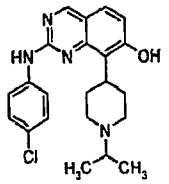
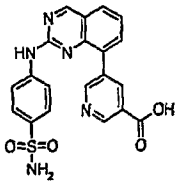
WO 2007/117607 PCT/US2007/008592

246		4-[8-(5-Pyrrolidin-1-ylmethyl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	461.1, 1.79					
247		4-[8-(5-Morpholin-4-ylmethyl-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	477.1, 1.79					
248		4-{8-[5-(4-Methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.70					
249		4-{8-[5-(3-Oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.76					
250		4-{7-(1-Methyl-1H-pyrazol-4-yl)-8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamid□e	570.2, 1.88					
251		4-{8-[5-(Isopropylamino-methyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	449.1, 1.78					

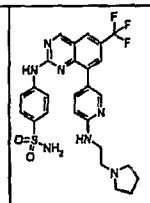
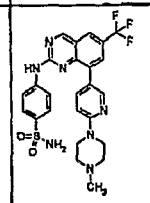
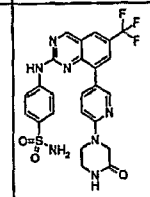
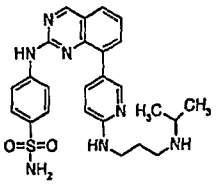
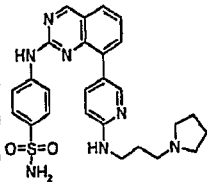
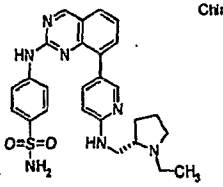
WO 2007/117607 PCT/US2007/008592

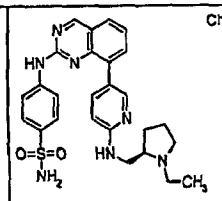
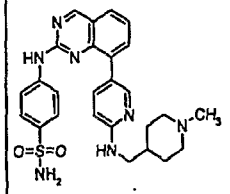
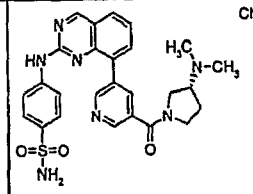
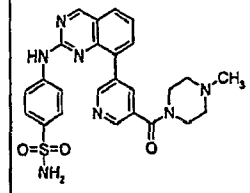
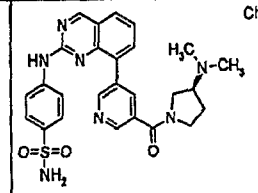
252		1-{5-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-pyridin-3-ylmethyl}-piperidine-4-carboxylic acid amide	518.1, 1.74					
253		4-(8-{5-[(Tetrahydro-pyran-4-ylamino)-methyl]-pyridin-3-yl}-quinazolin-2-ylamino)-benzenesulfonamide	491.1, 1.76					
254		4-{8-[5-(4-Acetyl-piperazin-1-ylmethyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	518.1, 1.77					
255		4-[8-(5-{[Methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-pyridin-3-yl)-quinazolin-2-ylamino]-benzenesulfonamide	505.1, 1.82					
256		4-{8-[6-((R)-3-Dimethylamino-pyrrolidin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.77					
257		4-{8-[6-((S)-3-Dimethylamino-pyrrolidin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.77					

WO 2007/117607 PCT/US2007/008592

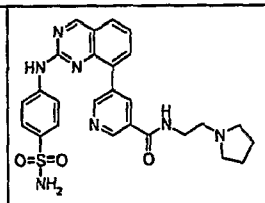
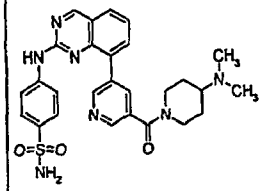
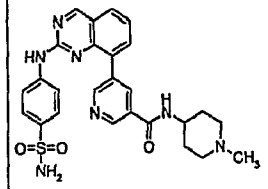
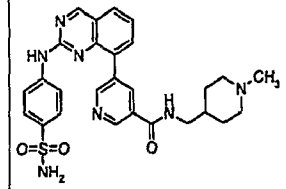
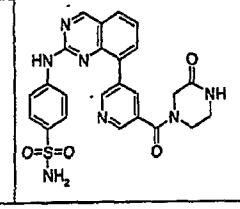
258		4-{8-[6-(2-Morpholin-4-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	506.1, 1.82					
259		4-{8-[6-(2-Diethylamino-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	492.1, 1.87					
260		4-{8-[6-(1-Methyl-piperidin-4-ylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	490.1, 1.82					
261		4-{8-[6-(4-Isopropyl-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	504.1, 1.92					
262		2-(4-Chloro-phenylamino)-8-(1-isopropyl-piperidin-4-yl)-quinazolin-7-ol	397.1, 2.53					
263		5-[2-(4-Sulfamoyl-phenylamino)-quinazolin-8-yl]-nicotinic acid	422.1, 1.94					

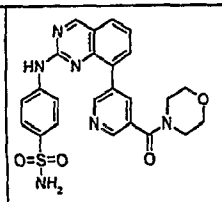
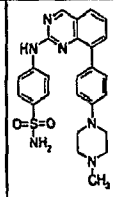
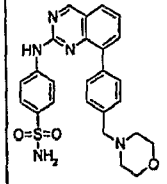
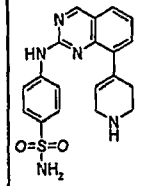
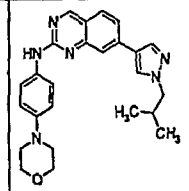
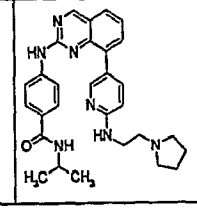
WO 2007/117607 PCT/US2007/008592

264		4-{8-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-6-trifluoromethyl-quinazolin-2-ylamino}-benzenesulfonamide	558.0, 2.11					
265		4-{8-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-yl]-6-trifluoromethyl-quinazolin-2-ylamino}-benzenesulfonamide	544.1, 2.20					
266		4-{8-[6-(3-Oxo-piperazin-1-yl)-pyridin-3-yl]-6-trifluoromethyl-quinazolin-2-ylamino}-benzenesulfonamide	544.1, 2.14					
267		4-{8-[6-(3-Isopropylamino-propylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	492.1, 1.87					
268		4-{8-[6-(3-Pyrrolidin-1-yl-propylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	504.1, 1.87					
269	Chiral 	4-(8-{6-[((S)-1-Ethyl-pyrrolidin-2-ylmethyl)-amino]-pyridin-3-yl}-quinazolin-2-ylamino)-benzenesulfonamide	504.1, 1.88					

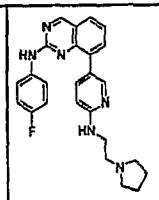
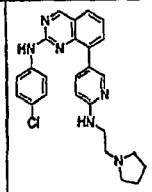
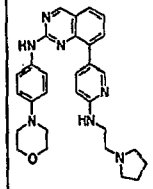
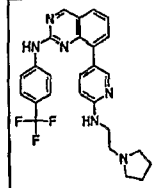
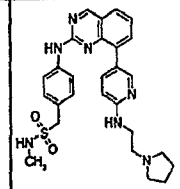
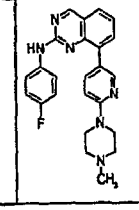
270	 Chiral	4-(8-{6-[((R)-1-Ethyl-pyrrolidin-2-ylmethyl)-amino]-pyridin-3-yl}-quinazolin-2-ylamino)-benzenesulfonamide	504.1, 2.00					
271		4-(8-{6-[(1-Methyl-piperidin-4-ylmethyl)-amino]-pyridin-3-yl}-quinazolin-2-ylamino)-benzenesulfonamide	504.1, 1.85					
272	 Chiral	4-{8-[5-((R)-3-Dimethylamino-pyrrolidine-1-carbonyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	518.2, 1.78					
273		4-{8-[5-(4-Methyl-piperazine-1-carbonyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	504.1, 1.79					
274	 Chiral	4-{8-[5-((S)-3-Dimethylamino-pyrrolidine-1-carbonyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	518.2, 1.77					

WO 2007/117607 PCT/US2007/008592

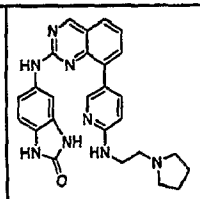
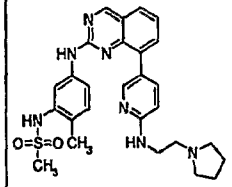
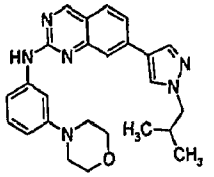
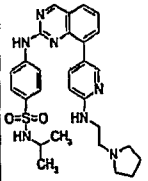
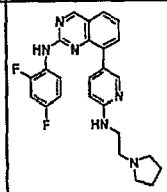
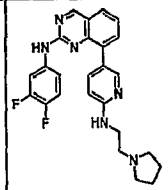
275		N-(2-Pyrrolidin-1-yl-ethyl)-5-[2-(4-sulfamoyl-phenylamino)-quinazolin-8-yl]-nicotinamide	518.2, 1.85					
276		4-{8-[5-(4-Dimethylamino-piperidine-1-carbonyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	532.1, 1.79					
277		N-(1-Methyl-piperidin-4-yl)-5-[2-(4-sulfamoyl-phenylamino)-quinazolin-8-yl]-nicotinamide	518.1, 1.79					
278		N-(1-Methyl-piperidin-4-ylmethyl)-5-[2-(4-sulfamoyl-phenylamino)-quinazolin-8-yl]-nicotinamide	532.1, 1.80					
279		4-{8-[5-(3-Oxo-piperazine-1-carbonyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	504.0, 1.83					

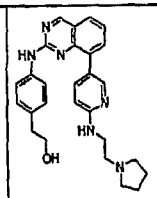
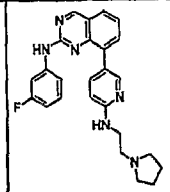
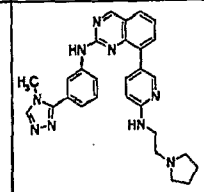
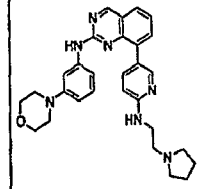
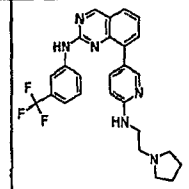
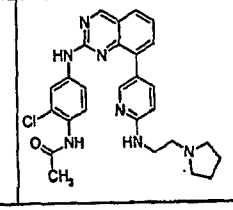
280		4-{8-[5-(Morpholine-4-carbonyl)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	491.1, 2.00					
281		4-{8-[4-(4-Methyl-piperazin-1-yl)-phenyl]-quinazolin-2-ylamino}-benzenesulfonamide	475.1, 2.22					
282		4-[8-(4-Morpholin-4-ylmethyl-phenyl)-quinazolin-2-ylamino]-benzenesulfonamide	476.1, 2.11					
283		4-[8-(1,2,3,6-Tetrahydro-pyridin-4-yl)-quinazolin-2-ylamino]-benzenesulfonamide	382.1, 1.88					
284		[7-(1-Isobutyl-1H-pyrazol-4-yl)-quinazolin-2-yl]-(4-morpholin-4-yl-phenyl)-amine	429.0, 2.898					
285		N-Isopropyl-4-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzamide	496.3, 1.71					

WO 2007/117607 PCT/US2007/008592

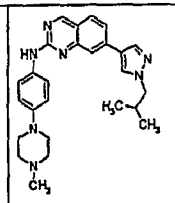
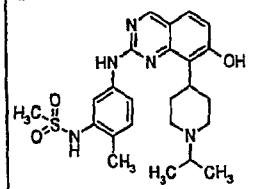
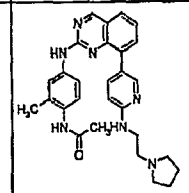
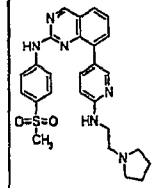
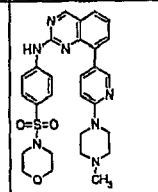
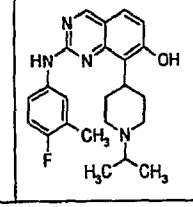
286		(4-Fluoro-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	429.1, 2.05					
287		(4-Chloro-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	445.1, 2.16					
288		(4-Morpholin-4-yl-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	496.2, 1.86					
289		{8-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-(4-trifluoromethyl-phenyl)-amine	479.1, 2.25					
290		N-Methyl-C-(4-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-phenyl)-methanesulfonamide	518.1, 1.91					
291		(4-Fluoro-phenyl)-{8-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-yl}-amine	415.1, 2.08					

WO 2007/117607 PCT/US2007/008592

292		5-{8-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one	467.4, 1.50					
293		N-(2-Methyl-5-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-phenyl)-methanesulfonamide	518.2, 1.69					
294		[7-(1-Isobutyl-1H-pyrazol-4-yl)-quinazolin-2-yl]-(3-morpholin-4-yl-phenyl)-amine	429.1, 3.148					
295		N-Isopropyl-4-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-benzenesulfonamide	532.1, 2.05					
296		(2,4-Difluoro-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	447.1, 2.02					
297		(3,4-Difluoro-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	447.1, 2.03					

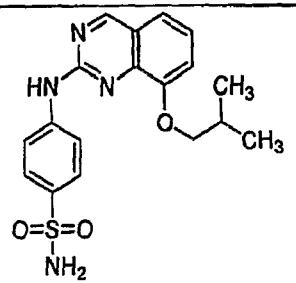
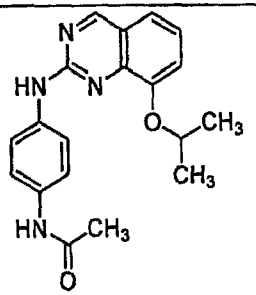
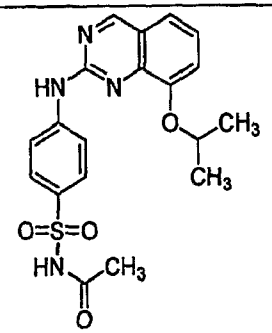
298		2-(4-{8-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-phenyl)-ethanol	455.2, 1.94					
299		(3-Fluoro-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	429.1, 2.07					
300		[3-(4-Methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	492.1, 1.87					
301		(3-Morpholin-4-yl-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	496.2, 1.98					
302		{8-[6-(2-Pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-(3-trifluoromethyl-phenyl)-amine	479.1, 2.29					
303		N-(2-Chloro-4-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-phenyl)-acetamide	502.1, 1.63					

WO 2007/117607 PCT/US2007/008592

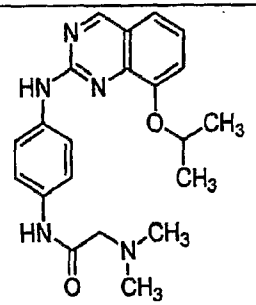
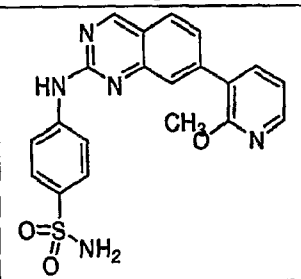
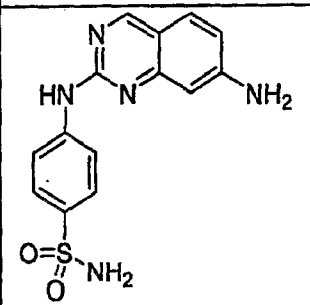
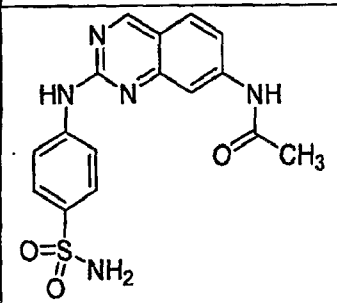
304		[7-(1-Isobutyl-1H-pyrazol-4-yl)-quinazolin-2-yl]-[4-(4-methyl-piperazin-1-yl)-phenyl]-amine	442.1, 3.526					
305		N-{5-[7-Hydroxy-8-(1-isopropyl-piperidin-4-yl)-quinazolin-2-ylamino]-2-methyl-phenyl}-methanesulfonamide	470.1, 2.17					
306		N-(2-Methyl-4-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-ylamino}-phenyl)-acetamide	482.2, 1.90					
307		(4-Methanesulfonyl-phenyl)-{8-[6-(2-pyrrolidin-1-yl-ethylamino)-pyridin-3-yl]-quinazolin-2-yl}-amine	489.1, 1.90					
308		{8-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-yl]-quinazolin-2-yl}-[4-(morpholine-4-sulfonyl)-phenyl]-amine	546.1, 2.09					
309		2-(4-Fluoro-3-methyl-phenylamino)-8-(1-isopropyl-piperidin-4-yl)-quinazolin-7-ol	395.2, 2.55					

WO 2007/117607 PCT/US2007/008592

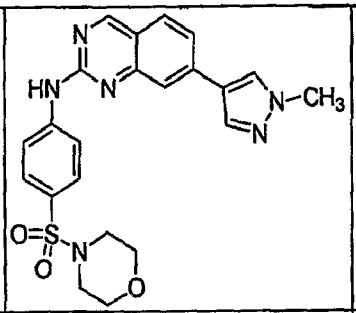
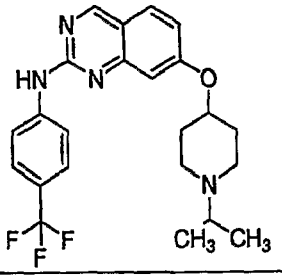
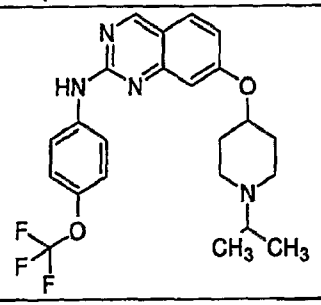
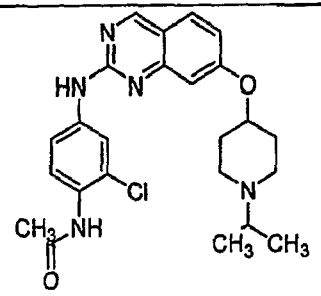
Table 3

Cmpd	Structure	Name	LC/MS (M+1(m/z), Rt(min))	Synthetic method	PDK1 IC_{50}	$CPEC_{50}$ A2780	$CPEC_{50}$ PC3	$CPEC_{50}$ PC3MM
310		4-(8-isobutoxyquinazolin-2-ylamino)benzenesulfonamide	373.1, 2.75	Similar to example 1	++++	++++		
311		N-(4-(8-isopropoxyquinazolin-2-ylamino)phenyl)acetamide	337.1, 2.18	Similar to example 1	++++	+++		
312		N-(4-(8-isopropoxyquinazolin-2-ylamino)phenylsulfonyl)acetamide	401.0, 2.60	Similar to example 1	++++	+++		

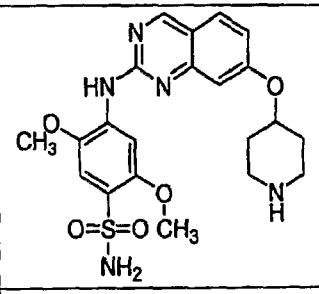
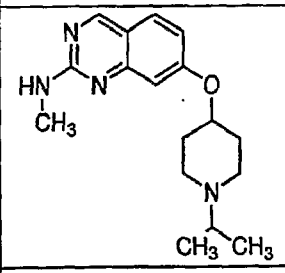
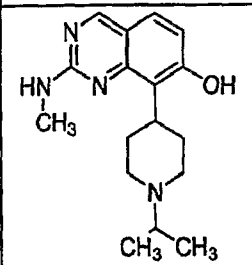
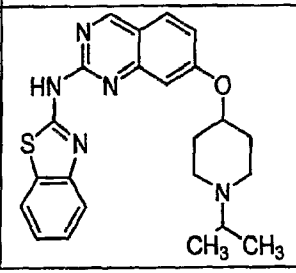
WO 2007/117607 PCT/US2007/008592

313		2-(dimethylamino)-N-(4-(8-isopropoxyquinazolin-2-ylamino)phenyl)acetamide	380.1, 1.95	Similar to example 1	+++	++++		
314		4-(7-(2-methoxypyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide	408.1, 3.10	Similar to example 39	+	+++		
315		4-(7-aminoquinazolin-2-ylamino)benzenesulfonamide	316.1, 1.61	Similar to example 43	++++	++++		
316		N-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)acetamide	358.0, 1.81	Similar to example 44	++++	++++		

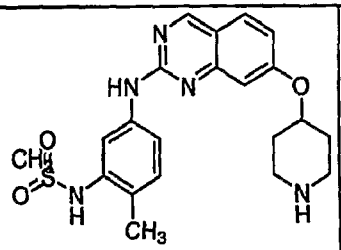
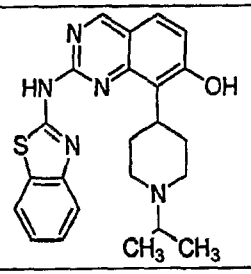
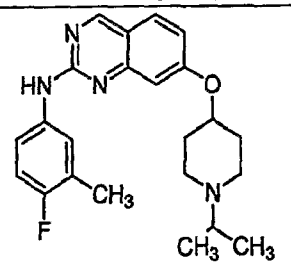
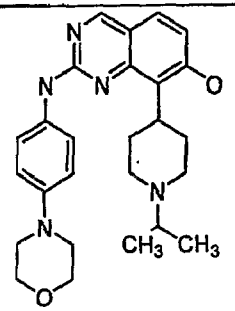
WO 2007/117607 PCT/US2007/008592

317		7-(1-methyl-1H-pyrazol-4-yl)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine	451.1, 2.53	Similar to example 39	+	++++		
318		7-(1-isopropylpiperidin-4-yloxy)-N-(4-(trifluoromethyl)phenyl)quinazolin-2-amine	431.1, 2.49	Similar to example 41	++++		++++	
319		7-(1-isopropylpiperidin-4-yloxy)-N-(4-(trifluoromethoxy)phenyl)quinazolin-2-amine	447.2, 2.51	Similar to example 41	++++		++++	
320		N-(2-chloro-4-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide	454.1, 1.99	Similar to example 41	++++		++++	

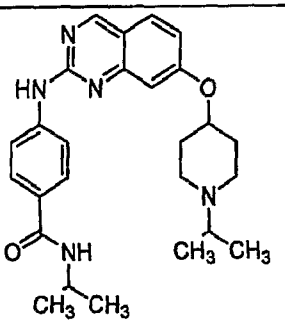
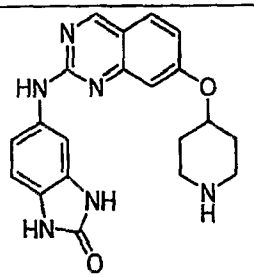
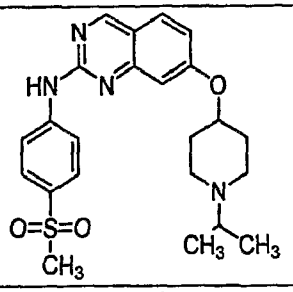
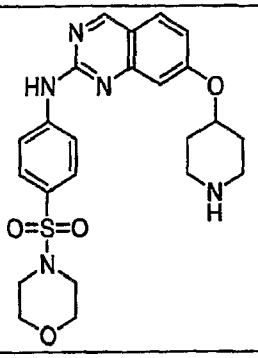
WO 2007/117607 PCT/US2007/008592

321		2,5-dimethoxy-4-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	460.1, 1.92	Similar to example 42	++++		+++	
322		7-(1-isopropylpiperidin-4-yloxy)-N-methylquinazolin-2-amine	301.1, 1.81	Similar to example 41	+		+++	
323		8-(1-isopropylpiperidin-4-yl)-2-(methylamino)quinazolin-7-ol	301.1, 1.40	Similar to example 41	+		+++	
324		N-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-yl)benzo[d]thiazol-2-amine	420.1, 2.16	Similar to example 41	+		++++	

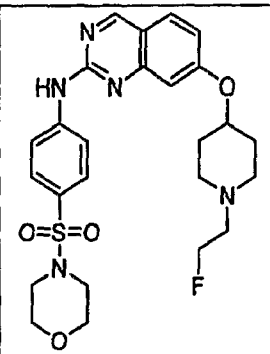
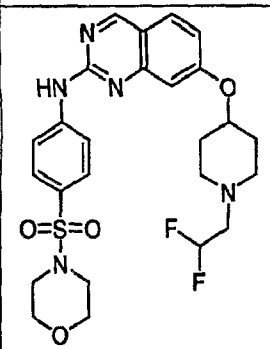
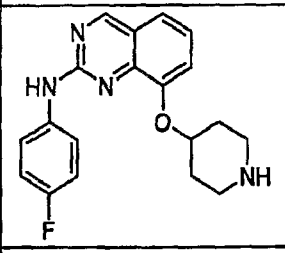
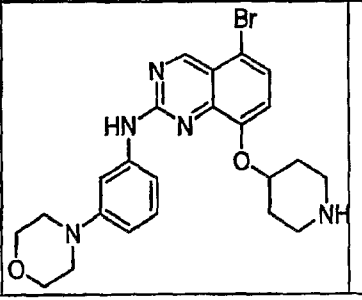
WO 2007/117607 PCT/US2007/008592

325		N-(2-methyl-5-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)methanesulfonamide	428.1, 1.81	Similar to example 37	++++		+++	
326		2-(benzo[d]thiazol-2-ylamino)-8-(1-isopropylpiperidin-4-yl)quinazolin-7-ol	420.1, 2.44	Similar to example 41	++++		+++	
327		N-(4-fluoro-3-methylphenyl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	395.2, 2.20	Similar to example 41	++++		+++	
328		8-(1-isopropylpiperidin-4-yl)-2-(4-morpholinophenylamino)quinazolin-7-ol	448.2, 2.01	Similar to example 41	++++		++++	

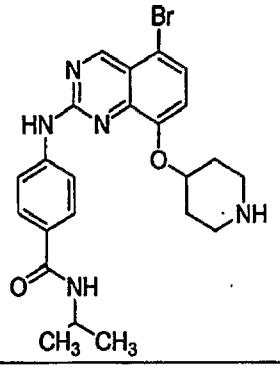
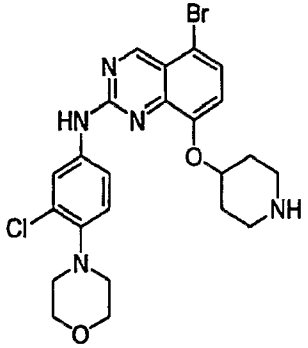
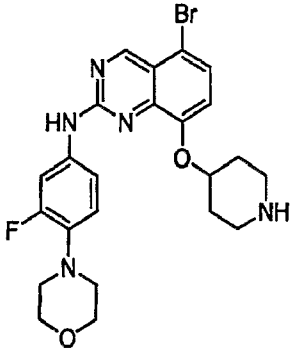
WO 2007/117607 PCT/US2007/008592

329		N-isopropyl-4-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzamide	448.1, 2.01	Similar to example 41	++++		++++	
330		5-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)-1H-benzo[d]imidazol-2(3H)-one	377.1, 1.51	Similar to example 42	++++		+++	
331		7-(1-isopropylpiperidin-4-yloxy)-N-(4-(methylsulfonyl)phenyl)quinazolin-2-amine	441.1, 2.05	Similar to example 41	++++		++++	
332		N-(4-(morpholinosulfonyl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	470.2, 2.09	Similar to example 37	++++		++++	

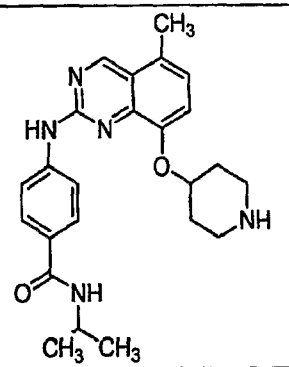
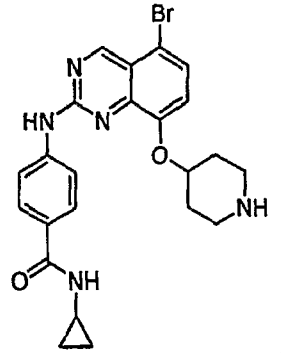
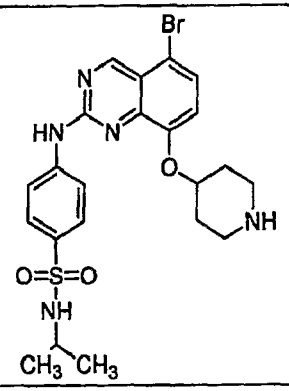
WO 2007/117607 PCT/US2007/008592

333		7-(1-(2-fluoroethyl)piperidin-4-yloxy)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine	516.1, 2.16	Similar to example 38	++++		++++	
334		7-(1-(2,2-difluoroethyl)piperidin-4-yloxy)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine	534.1, 2.14	Similar to example 38	++++		+++	
335		N-(4-fluorophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	339.1, 2.01	Similar to example 1	++++		++++	
336		5-bromo-N-(3-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	484.1 / 486.1, 2.18	Similar to example 45	++++		+++	

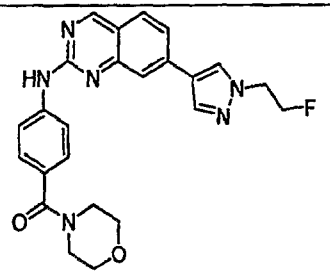
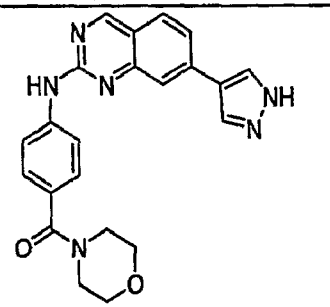
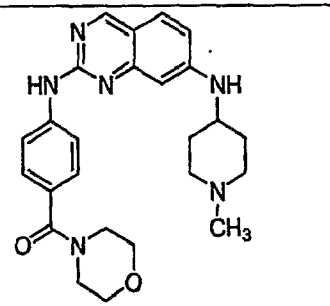
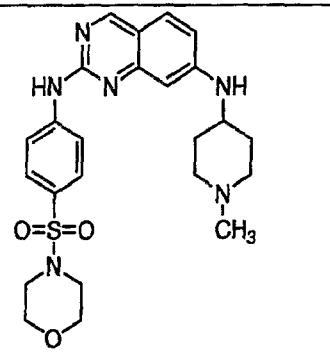
WO 2007/117607 PCT/US2007/008592

337		4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzamide	484.1 / 486.1, 2.29	Similar to example 45	++++		++++	
338		5-bromo-N-(3-chloro-4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	518.0 / 520.0, 2.49	Similar to example 45	++++		++++	
339		5-bromo-N-(3-fluoro-4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	502.1 / 504.1, 2.34	Similar to example 45	++++		++++	

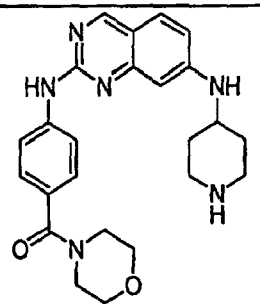
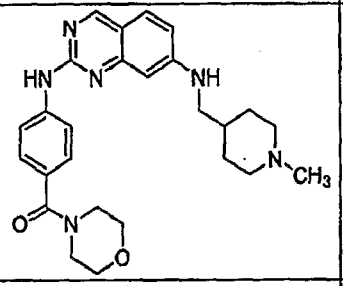
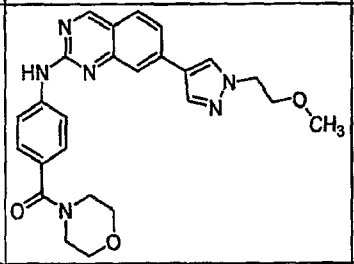
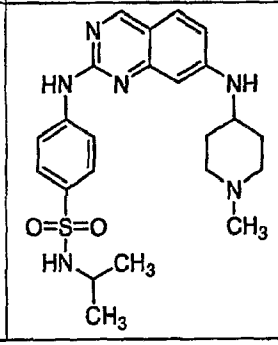
WO 2007/117607 PCT/US2007/008592

340		N-isopropyl-4-(5-methyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	420.2, 2.14	Similar to example 46	++++		+++	
341		4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-cyclopropylbenzamide	482.1 / 484.1, 2.27	Similar to example 45	++++		+++	
342		4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzenesulfonamide	520.0 / 522.0, 2.42	Similar to example 45	++++		++++	

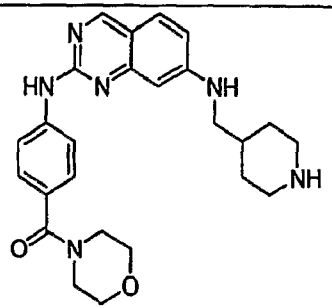
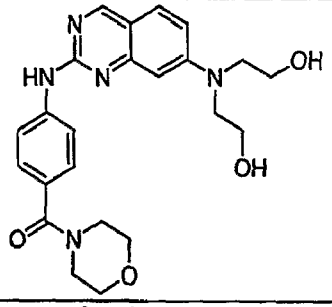
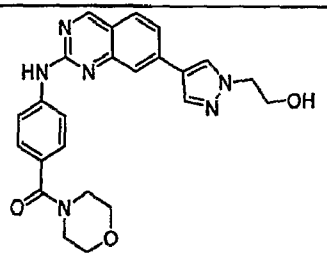
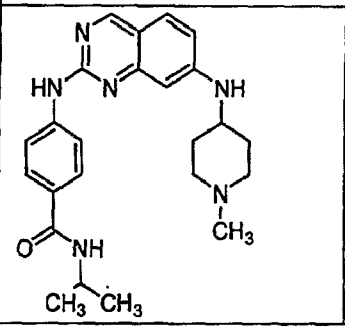
WO 2007/117607 PCT/US2007/008592

343		(4-(7-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	447.2, 2.16	Similar to example 39	++++		++++	
344		(4-(7-(1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	401.1, 1.90	Similar to example 39	++++		++++	
345		(4-(7-(1-methylpiperidin-4-ylamino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	447.1, 1.68	Similar to example 40	++++		++++	
346		N7-(1-methylpiperidin-4-yl)-N2-(4-(morpholinosulfonyl)phenyl)quinazoline-2,7-diamine	483.2, 1.88	Similar to example 40	++++		++++	

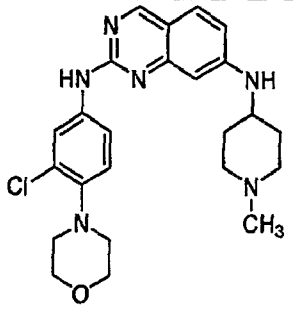
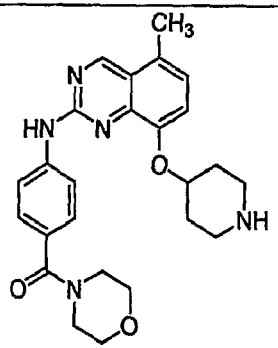
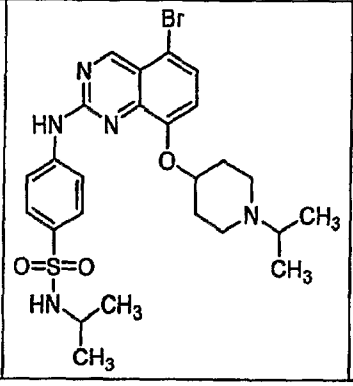
WO 2007/117607 PCT/US2007/008592

347		morpholino(4-(7-(piperidin-4-ylamino)quinazolin-2-ylamino)phenyl)methanone	433.1, 1.62	Similar to example 40	++++		++++	
348		(4-(7-((1-methylpiperidin-4-yl)methylamino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	461.2, 1.66	Similar to example 40	++++		+++	
349		(4-(7-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	459.1, 2.14	Similar to example 39	++++		++++	
350		N-isopropyl-4-(7-(1-methylpiperidin-4-ylamino)quinazolin-2-ylamino)benzenesulfonamide	455.1, 1.90	Similar to example 40	++++		++++	

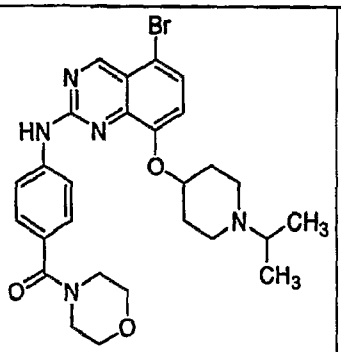
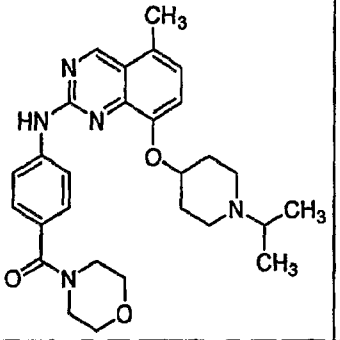
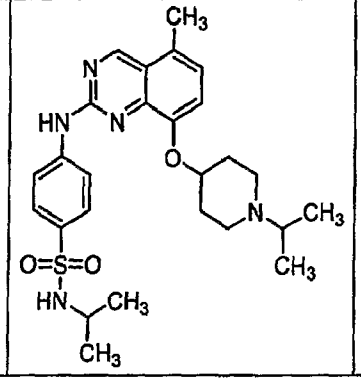
WO 2007/117607 PCT/US2007/008592

351		morpholino(4-(7-(piperidin-4-ylmethylamino)quinazolin-2-ylamino)phenyl)methanone	447.2, 1.64	Similar to example 40	++++		+++	
352		(4-(7-(bis(2-hydroxyethyl)amino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	438.1, 1.66	Similar to example 40	++++		+++	
353		(4-(7-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	445.1, 1.90	Similar to example 39	++++		+++	
354		N-isopropyl-4-(7-(1-methylpiperidin-4-ylamino)quinazolin-2-ylamino)benzamide	419.2, 1.81	Similar to example 40	++++		++++	

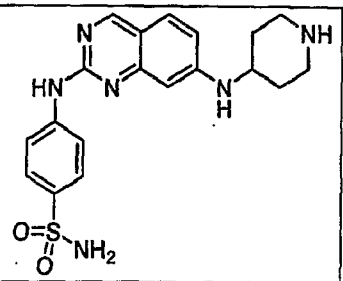
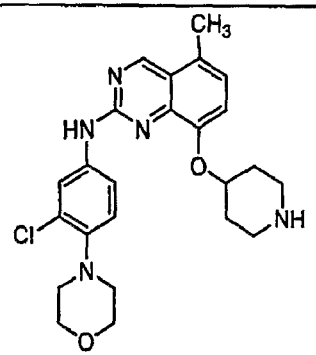
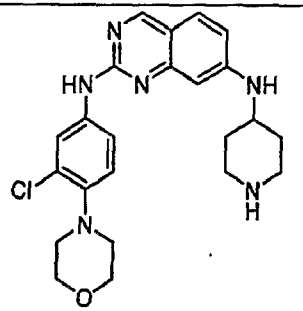
WO 2007/117607 PCT/US2007/008592

355		N2-(3-chloro-4-morpholinophenyl)-N7-(1-methylpiperidin-4-yl)quinazoline-2,7-diamine	453.2, 2.01	Similar to example 40	++++		++++	
356		(4-(5-methyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	448.2, 1.97	Similar to example 46	++++		+++	
357		4-(5-bromo-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzenesulfonamide	562.1 / 564.1, 2.44	Similar to example 45	++++		++++	

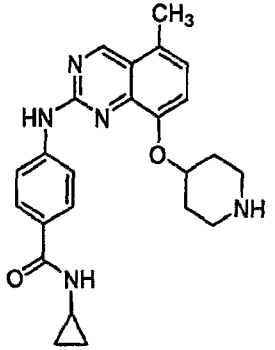
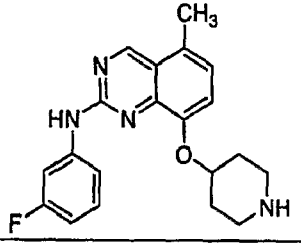
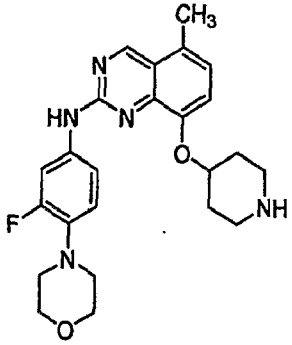
WO 2007/117607 PCT/US2007/008592

358		(4-(5-bromo-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	554.2 / 556.1, 2.31	Similar to example 45	++++		+++	
359		(4-(8-(1-isopropylpiperidin-4-yloxy)-5-methylquinazolin-2-ylamino)phenyl)(morpholino)methanone	490.2, 2.03	Similar to example 46	++++		+++	
360		N-isopropyl-4-(8-(1-isopropylpiperidin-4-yloxy)-5-methylquinazolin-2-ylamino)benzenesulfonamide	498.2, 2.44	Similar to example 46	++++		++++	

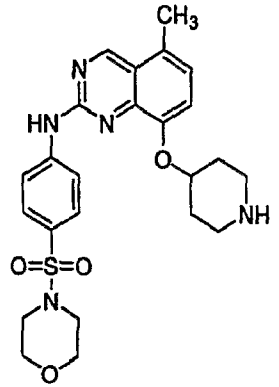
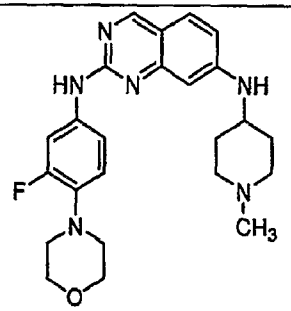
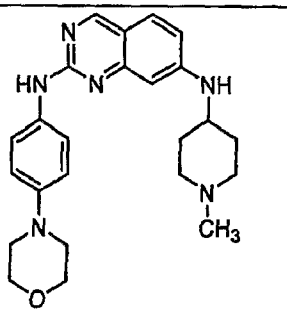
WO 2007/117607 PCT/US2007/008592

361		4-(7-(piperidin-4-ylamino)quinazolin-2-ylamino)benzenesulfonamide	399.1, 1.51	Similar to example 40	++++		+++	
362		N-(3-chloro-4-morpholinophenyl)-5-methyl-8-(piperidin-4-yloxy)quinazolin-2-amine	454.2, 2.29	Example 46	++++		++++	
363		N2-(3-chloro-4-morpholinophenyl)-N7-(piperidin-4-yl)quinazoline-2,7-diamine	439.1, 1.88	Similar to example 40	++++		++++	

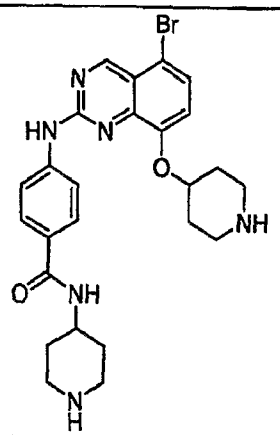
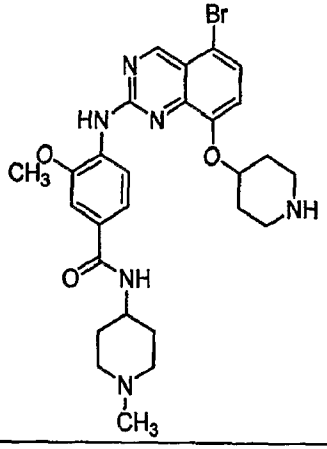
WO 2007/117607 PCT/US2007/008592

364		N-cyclopropyl-4-(5-methyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	418.2, 2.07	Similar to example 46	++++	++++	++++	
365		N-(3-fluorophenyl)-5-methyl-8-(piperidin-4-yloxy)quinazolin-2-amine	353.2, 2.25	Similar to example 46	++++		+++	
366		N-(3-fluoro-4-morpholinophenyl)-5-methyl-8-(piperidin-4-yloxy)quinazolin-2-amine	438.2, 2.14	Similar to example 46	++++		+++	

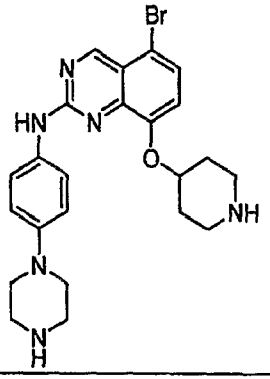
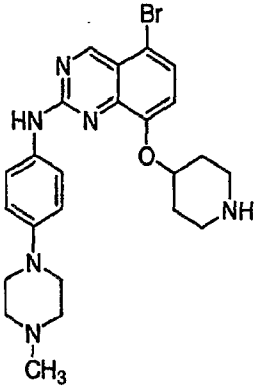
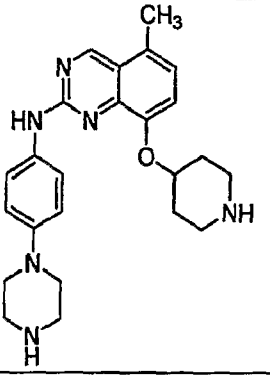
WO 2007/117607 PCT/US2007/008592

367		5-methyl-N-(4-(morpholinosulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	484.1, 2.19	Similar to example 46	++++		+++	
368		N2-(3-fluoro-4-morpholinophenyl)-N7-(1-methylpiperidin-4-yl)quinazoline-2,7-diamine	437.3, 1.96	Similar to example 40	++++		++++	
369		N7-(1-methylpiperidin-4-yl)-N2-(4-morpholinophenyl)quinazoline-2,7-diamine	419.2, 1.77	Similar to example 40	++++		+++	

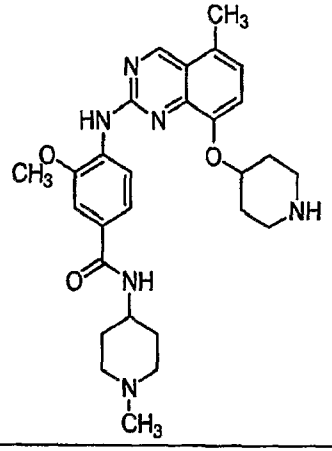
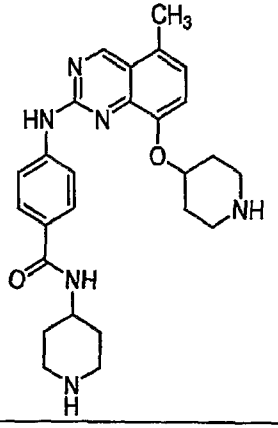
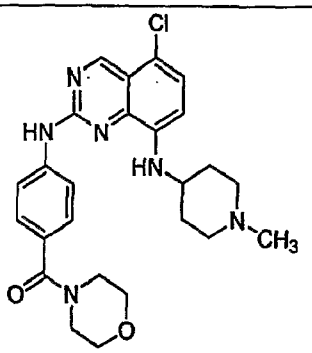
WO 2007/117607 PCT/US2007/008592

370		4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(piperidin-4-yl)benzamide	525.2 / 527.2, 2.18	Similar to example 45	+		+++	
371		4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide	569.1 / 571.1, 2.07	Similar to example 47	+		+++	

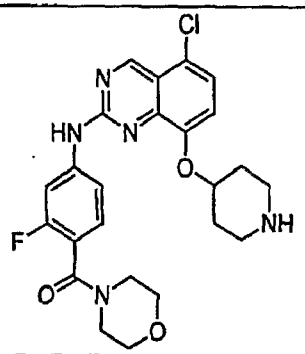
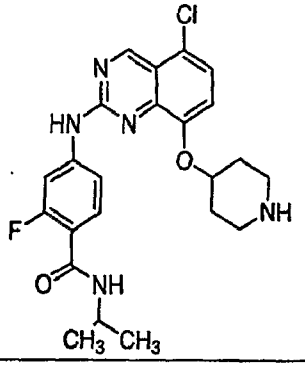
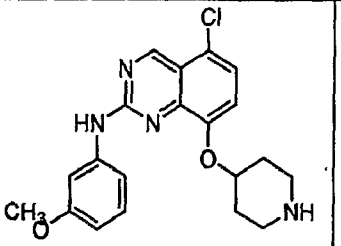
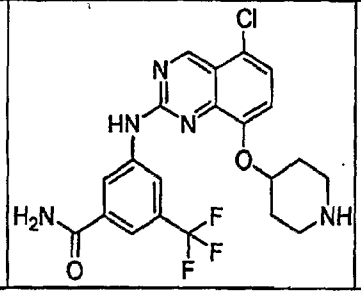
WO 2007/117607 PCT/US2007/008592

372		5-bromo-N-(4-(piperazin-1-yl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	483.1 / 485.1, 2.10	Similar to example 45	+		++++	
373		5-bromo-N-(4-(4-methylpiperazin-1-yl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	496.2 / 498.2, 2.18	Similar to example 45	++		++++	
374		5-methyl-N-(4-(piperazin-1-yl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	419.2, 1.88	Similar to example 46	+		+++	

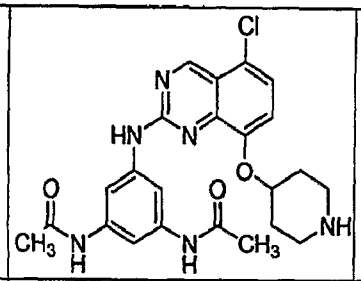
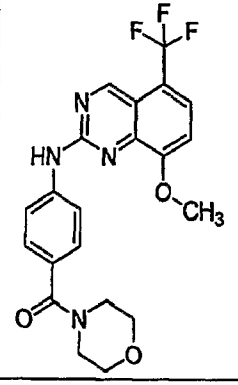
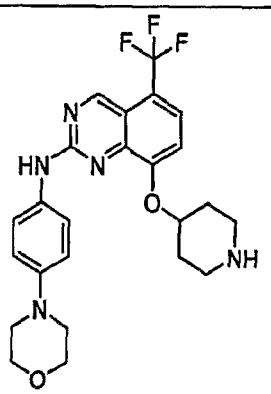
WO 2007/117607 PCT/US2007/008592

375		3-methoxy-4-(5-methyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(1-methylpiperidin-4-yl)benzamide	505.2, 1.97	Similar to example 46	+++		+++	
376		4-(5-methyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(piperidin-4-yl)benzamide	461.3, 1.83	Similar to example 46	+		+++	
377		(4-(5-chloro-8-(1-methylpiperidin-4-ylamino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	481.2, 2.27	Similar to example 50	++++		++++	

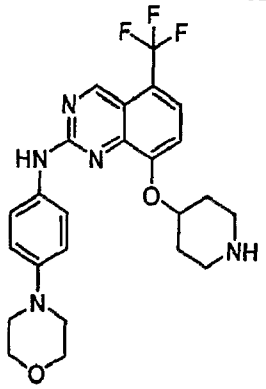
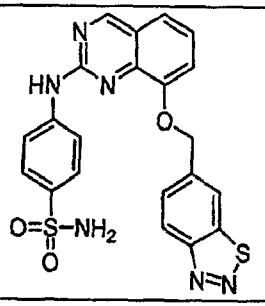
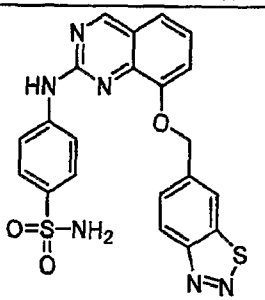
WO 2007/117607 PCT/US2007/008592

378		(4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-2-fluorophenyl)(morpholino)methanone	486.1, 2.25	Similar to example 48	++++		++++	
379		4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-2-fluoro-N-isopropylbenzamide	458.2, 2.40	Similar to example 48	++++		++++	
380		5-chloro-N-(3-methoxyphenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	385.2, 2.44	Similar to example 32	++++		++++	
381		3-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(trifluoromethyl)benzamide	466.1, 2.36	Similar to example 32	++++		++++	

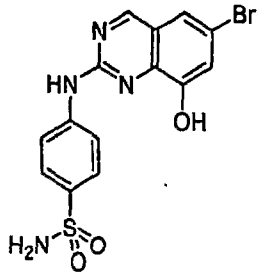
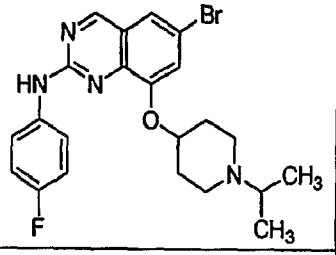
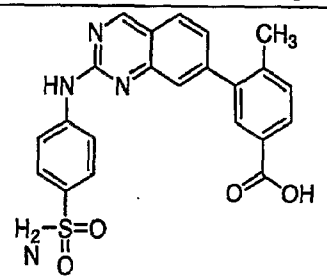
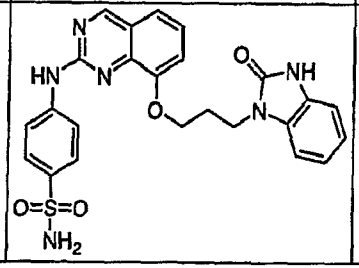
WO 2007/117607 PCT/US2007/008592

382		N,N'-(5-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-1,3-phenylene)diacetamide	469.2, 1.99	Similar to example 32	++++		+++	
383		(4-(8-methoxy-5-(trifluoromethyl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	433.2, 2.59	Similar to example 51	++++		+++	
384		N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)-5-(trifluoromethyl)quinazolin-2-amine	502.2, 2.29	Similar to example 52	++++		+++	

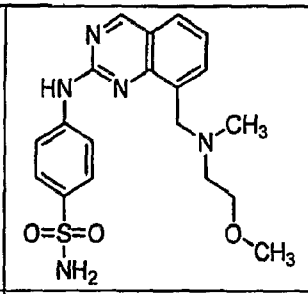
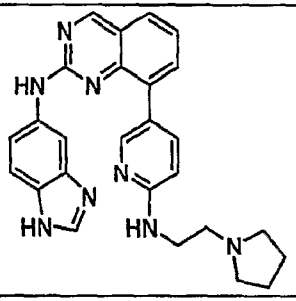
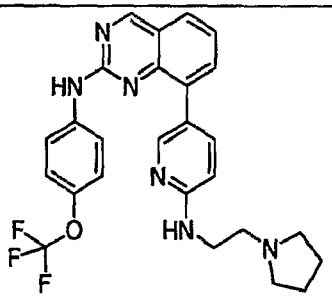
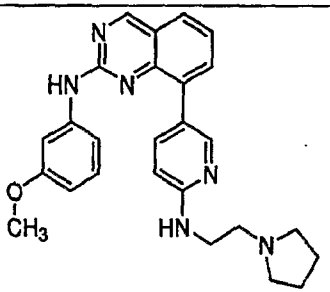
WO 2007/117607 PCT/US2007/008592

385		N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)-5-(trifluoromethyl)quinazolin-2-amine	474.2, 2.16	Similar to example 52	++++		++++	
386		4-(8-(benzo[d][1,2,3]thiadiazol-6-ylmethoxy)quinazolin-2-ylamino)benzenesulfonamide	465	Similar to example 1	++++	++++		
387		4-(8-(benzo[d][1,2,3]thiadiazol-6-ylmethoxy)quinazolin-2-ylamino)benzenesulfonamide	365, 2.10	Similar to example 1, using 1-(methylsulfonyl)piperazine for SNAR step and 2-proponol for Mitsunobu	++++	++++		

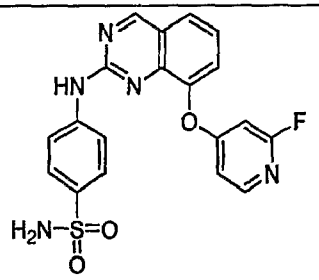
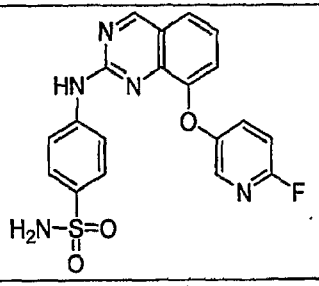
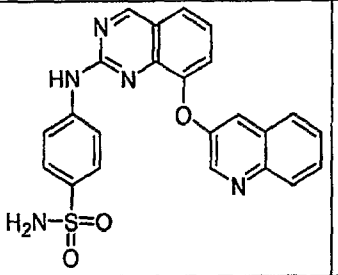
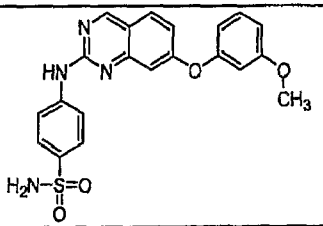
WO 2007/117607 PCT/US2007/008592

388		4-(6-bromo-8-hydroxyquinazolin-2-ylamino)benzenesulfonamide	395/397, 2.53	Similar to example 1, steps 1 and 2	++++	++++		
389		6-bromo-N-(4-fluorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	459/461	Similar to example 1, using 4-fluoroaniline for SNAR and 4-hydroxy-1-isopropylpiperidine for Mitsunobu	++++		++++	
390		4-methyl-3-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzoic acid	435, 2.50	Similar to example 25, using 5-carboxy-2-methylbenzeneboronic acid in step 7	++++		+++	
391		4-(8-(3-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)propoxy)quinazolin-2-ylamino)benzenesulfonamide	491.2, 2.20	Similar to example 2 and example 32, step 3	++++	+++		

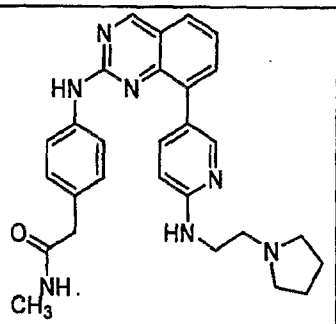
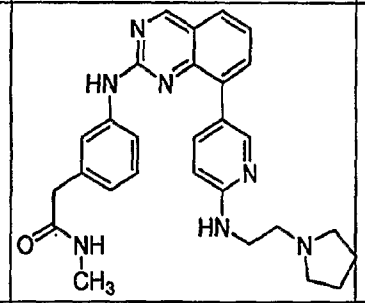
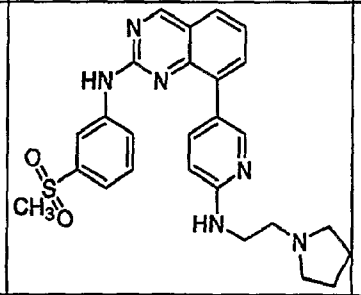
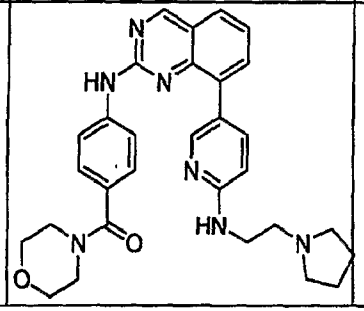
WO 2007/117607 PCT/US2007/008592

392		4-(8-(((2-methoxyethyl)(methyl)amino)methyl) quinazolin-2-ylamino)benzenesulfonamide	402.2, 1.69	Similar to example 54	++++	++++		
393		N-(1H-benzo[d]imidazol-5-yl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	451.1, 1.74	Similar to example 2 and example 55	++++		++++	
394		8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-N-(4-(trifluoromethoxy)phenyl)quinazolin-2-amine	479.2, 2.03	Similar to example 2 and example 55	++++		++++	
395		N-(3-methoxyphenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	441.1, 2.02	Similar to example 2 and example 55	++++		++++	

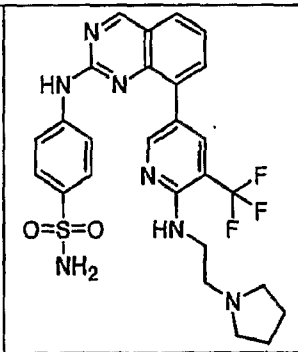
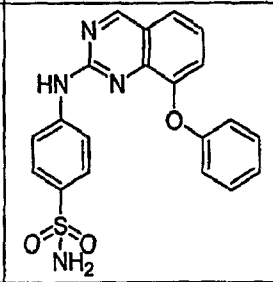
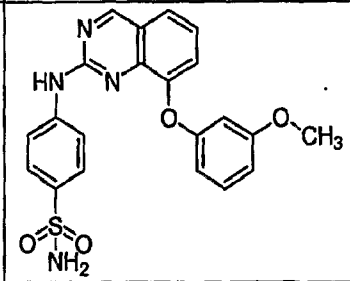
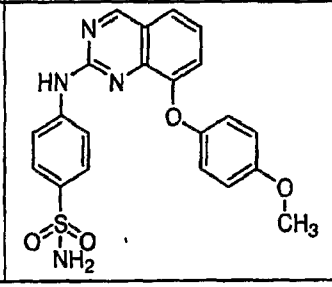
WO 2007/117607 PCT/US2007/008592

412		4-(8-(2-fluoropyridin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	412, 2.48	Similar to example 57	++++			
413		4-(8-(6-fluoropyridin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide	412, 2.53	Similar to example 57	++++		++++	
414		4-(8-(quinolin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide	444, 2.33	Similar to example 57	+			
415		4-(7-(3-methoxyphenoxy)quinazolin-2-ylamino)benzenesulfonamide	423, 2.81	Similar to example 58	++++	++++		

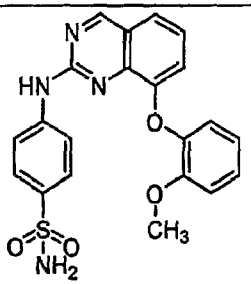
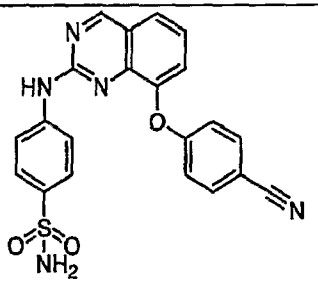
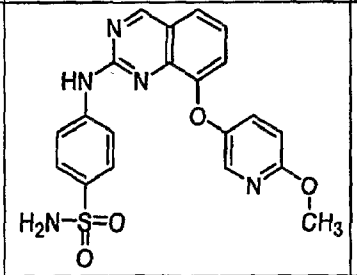
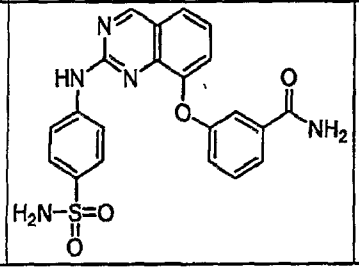
WO 2007/117607 PCT/US2007/008592

400		N-methyl-2-(4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide	482.2, 1.85	Similar to example 2 and example 55	++++		++++	
401		N-methyl-2-(3-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide	482.2, 1.84	Similar to example 2 and example 55	++++		++++	
402		N-(3-(methylsulfonyl)phenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	489.2, 1.63	Similar to example 2 and example 55	++++		+++	
403		morpholino(4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)methanone	524.2, 1.93	Similar to example 2 and example 55	++++		++++	

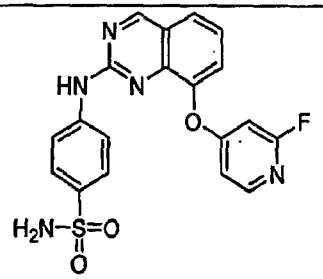
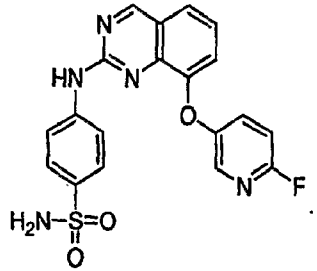
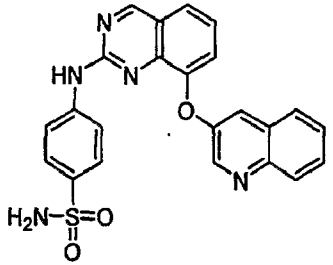
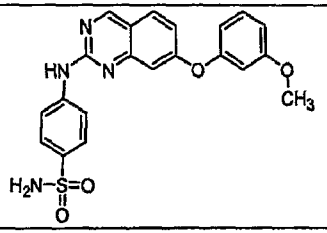
WO 2007/117607 PCT/US2007/008592

404		4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)-5-(trifluoromethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide	558.0, 2.36	Similat to example 2 and example 55	++++		++++	
405		4-(8-phenoxyquinazolin-2-ylamino)benzenesulfonamide	393, 2.70	Similar to example 57	++++	++++	++++	
406		4-(8-(3-methoxyphenoxy)quinazolin-2-ylamino)benzenesulfonamide	423, 2.72	Similar to example 57	++++	++++		
407		4-(8-(4-methoxyphenoxy)quinazolin-2-ylamino)benzenesulfonamide	423, 2.77	Similar to example 57	++++	++++		

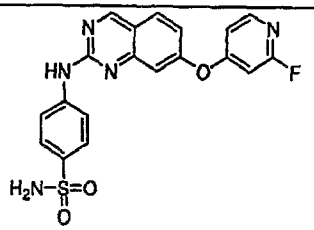
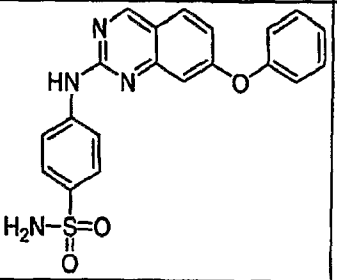
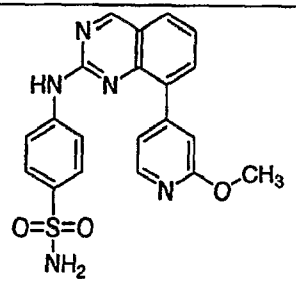
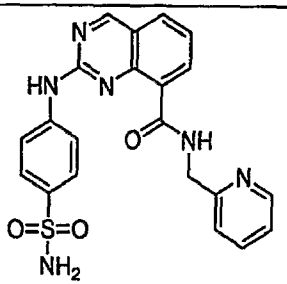
WO 2007/117607 PCT/US2007/008592

408		4-(8-(2-methoxyphenoxy)quinazolin-2-ylamino)benzenesulfonamide	423, 2.70	Similar to example 57	++++			
409		4-(8-(4-cyanophenoxy)quinazolin-2-ylamino)benzenesulfonamide	418, 2.64	Similar to example 57	++++	+++		
410		4-(8-(6-methoxypyridin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide	424, 2.11	Similar to example 57	++++		++++	
411		3-(2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)benzamide	436, 2.26	Similar to example 57	++++			

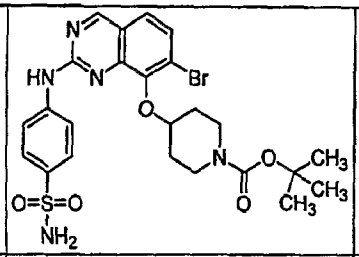
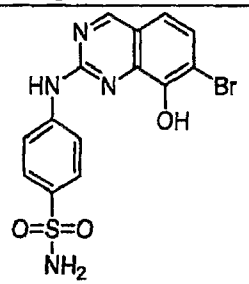
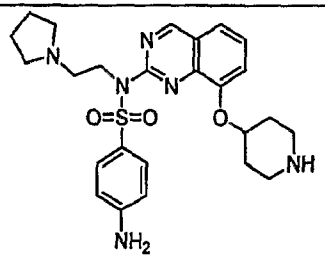
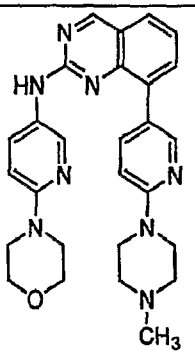
WO 2007/117607 PCT/US2007/008592

412		4-(8-(2-fluoropyridin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	412, 2.48	Similar to example 57	++++			
413		4-(8-(6-fluoropyridin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide	412, 2.53	Similar to example 57	++++		++++	
414		4-(8-(quinolin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide	444, 2.33	Similar to example 57	+			
415		4-(7-(3-methoxyphenoxy)quinazolin-2-ylamino)benzenesulfonamide	423, 2.81	Similar to example 58	++++	++++		

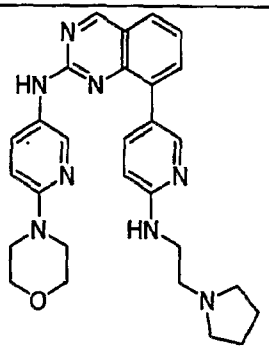
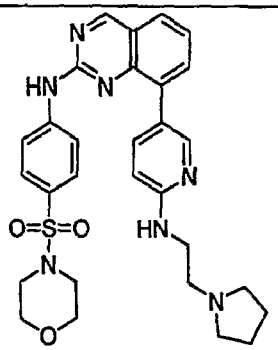
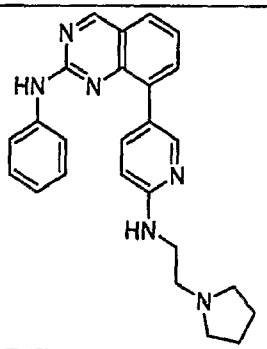
WO 2007/117607 PCT/US2007/008592

416		4-(7-(2-fluoropyridin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	412, 2.51	Similar to example 58	++++			
417		4-(7-phenoxyquinazolin-2-ylamino)benzenesulfonamide		Similar to example 58	+			
418		4-(8-(2-methoxypyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide	408.0, 2.30	Suzuki (see example 8 step 1) Then example 56	+			
419		N-(pyridin-2-ylmethyl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide	435.0, 1.82		+	+++		

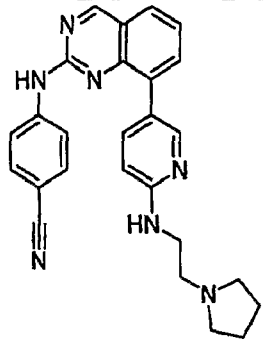
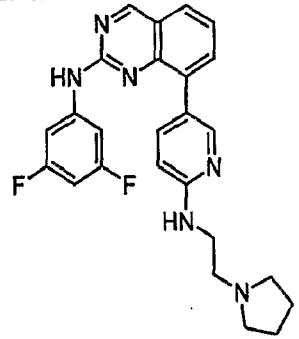
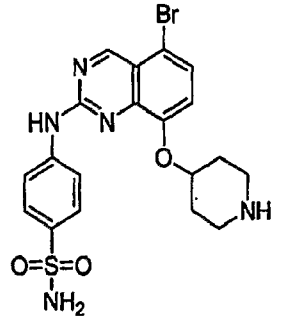
WO 2007/117607 PCT/US2007/008592

420		tert-butyl 4-(7-bromo-2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)piperidine-1-carboxylate	578.0/580.0, 3.24	Similar to example 7	+	++++		
421		4-(7-bromo-8-hydroxyquinazolin-2-ylamino)benzenesulfonamide	394.9/396.9, 2.51	example 5 then example 9 step 3	+++	++++		
422		4-amino-N-(8-(piperidin-4-yloxy)quinazolin-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)benzenesulfonamide	497.2, 1.73	example 7 with 5.5eq of KOtBu 110c 50 hrs, then example 8 step2	+++		+++	
423		8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-N-(6-morpholinopyridin-3-yl)quinazolin-2-amine	483.1, 1.75	Suzuki (see example 8 step 1)	++++		++++	

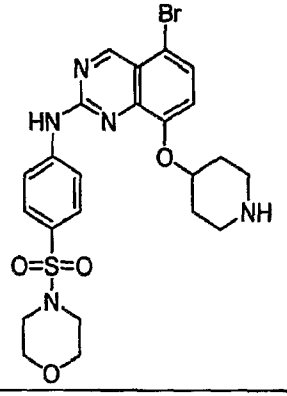
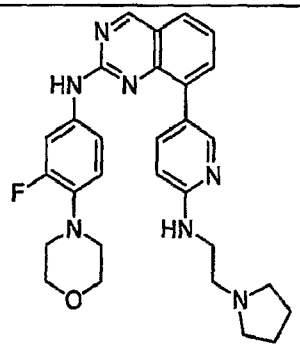
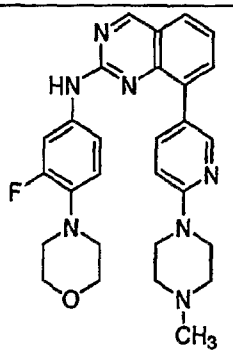
WO 2007/117607 PCT/US2007/008592

424		N-(6-morpholinopyridin-3-yl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	497.2, 1.75	Suzuki (see example 8 step 1)	++++		++++	
425		N-(4-(morpholinosulfonyl)phenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridine-3-yl)quinazolin-2-amine	560.2, 2.04	Suzuki (see example 8 step 1)	++++		++++	
426		N-phenyl-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	411.2, 2.02	Suzuki (see example 8 step 1)	++++		++++	

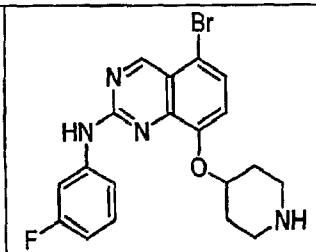
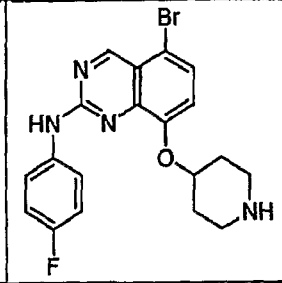
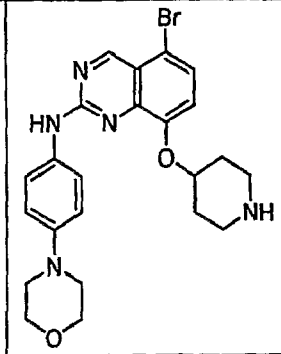
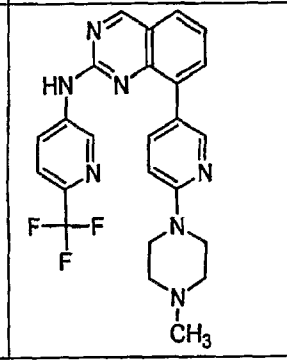
WO 2007/117607 PCT/US2007/008592

427		4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzonitrile	436.1, 2.03	Suzuki (see example 8 step 1)	++++		++++	
428		N-(3,5-difluorophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	447.1, 2.11	Suzuki (see example 8 step 1)	++++		++++	
429		4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	478.0/480.0, 2.16	example 9 step 3 then example 8 step2	++++		+++	

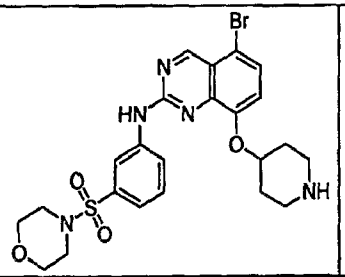
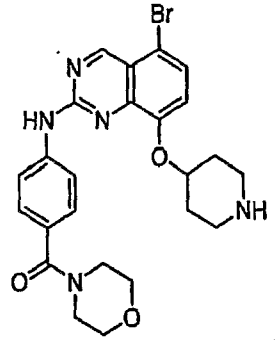
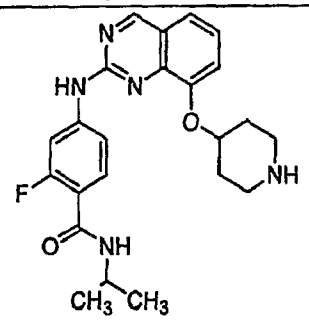
WO 2007/117607 PCT/US2007/008592

430		5-bromo-N-(4-(morpholinosulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	548.0/550.0, 2.39	example 9 step 3 then example 8 step2	++++		++++	
431		N-(3-fluoro-4-morpholinophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridine-3-yl)quinazolin-2-amine	514.2, 2.02	Suzuki (see example 8 step 1	++++		++++	
432		N-(3-fluoro-4-morpholinophenyl)-8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-amine	500.2, 2.03	Suzuki (see example 8 step 1	++++		++++	

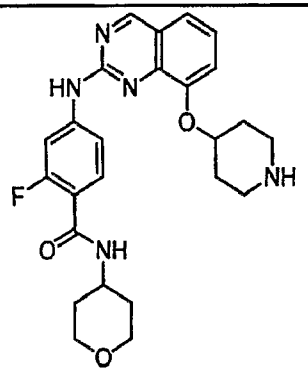
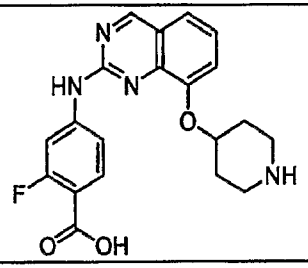
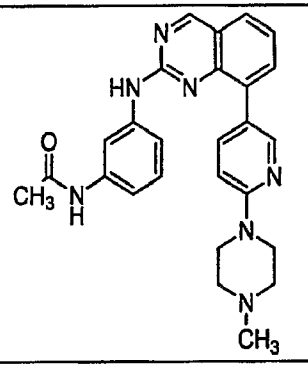
WO 2007/117607 PCT/US2007/008592

433		5-bromo-N-(3-fluorophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	417.0/419.0, 2.50	example 9 step 3 then example 8 step2	++++		++++	
434		5-bromo-N-(4-fluorophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	417.0/419.0, 2.46	example 9 step 3 then example 8 step2	++++		++++	
435		5-bromo-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	484.0/486.0, 2.05	example 9 step 3 then example 8 step2	++++		+++	
436		8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-N-(6-(trifluoromethyl)pyridine-3-yl)quinazolin-2-amine	466.1, 2.10	Suzuki (see example 8 step 1)	++++		++++	

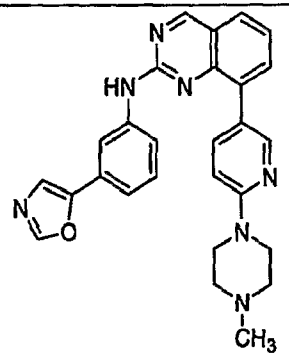
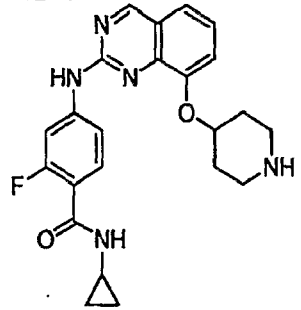
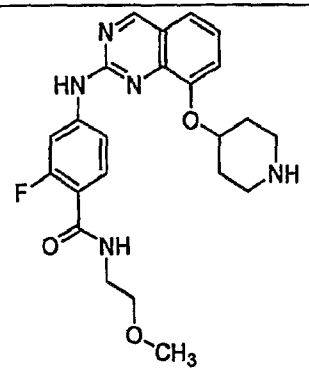
WO 2007/117607 PCT/US2007/008592

437		5-bromo-N-(3-(morpholinosulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	548.0/550.0, 2.40	example 9 step 3 then example 8 step2	+++		++++	
438		(4-(5-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	512.1/514.1, 2.23	example 9 step 3 then example 8 step2	++++		++++	
439		2-fluoro-N-isopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	424.2, 2.18		++++		++++	

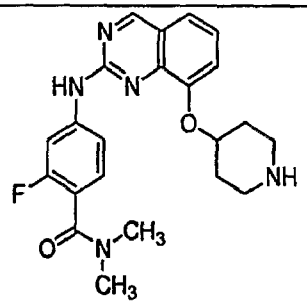
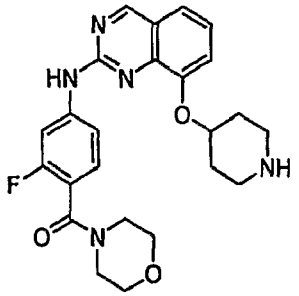
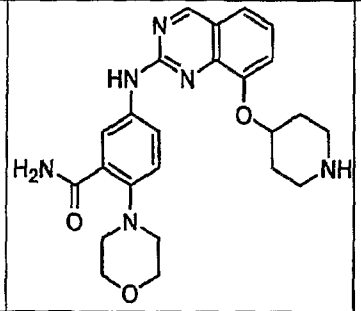
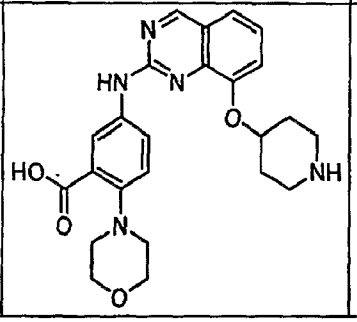
WO 2007/117607 PCT/US2007/008592

440		2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(tetrahydro-2H-pyran-4-yl)benzamide	466.2, 2.05		++++		++++	
441		2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoic acid	383.0, 2.02	example 9 step 3 then example 8 step2	++++		+++	
442		N-(3-(8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide	454.1, 1.88	Suzuki (see example 8 step 1)	++++		++++	

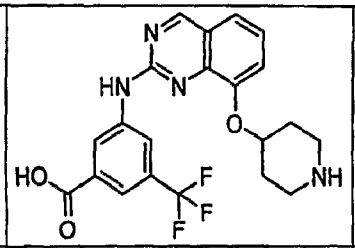
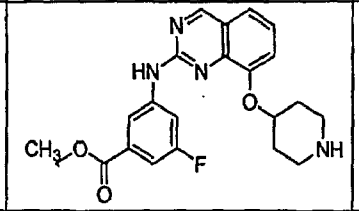
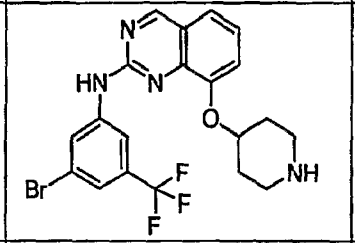
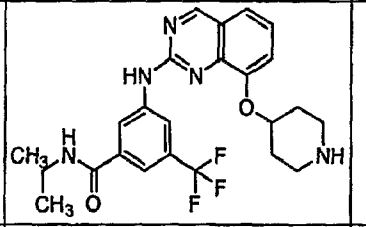
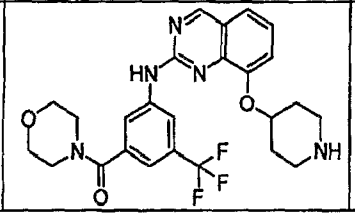
WO 2007/117607 PCT/US2007/008592

443		8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-N-(3-(oxazol-5-yl)phenyl)quinazolin-2-amine	464.1, 2.08	Suzuki (see example 8 step 1)	++++		++++	
444		N-cyclopropyl-2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	422.1, 2.08		++++		++++	
445		2-fluoro-N-(2-methoxyethyl)-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	440.1, 2.02		++++		++++	

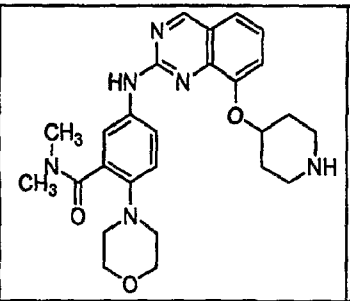
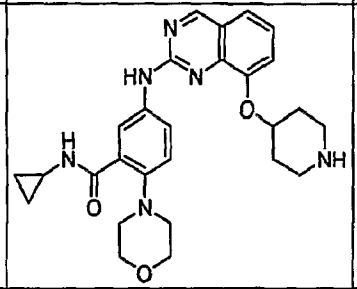
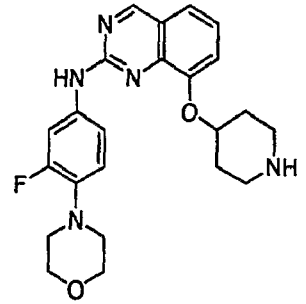
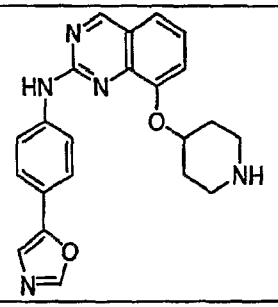
WO 2007/117607 PCT/US2007/008592

446		2-fluoro-N,N-dimethyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	410.1, 2.03		++++		++++	
447		(2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	452.1, 2.01		++++		++++	
448		2-morpholino-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	449.1, 1.77	example 9 step 3 then example 8 step2	++++		+++	
449		2-morpholino-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoic acid	450.2, 1.82	example 9 step 3 then example 8 step2	++++		+++	

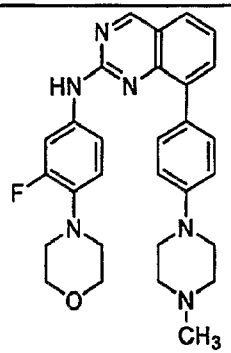
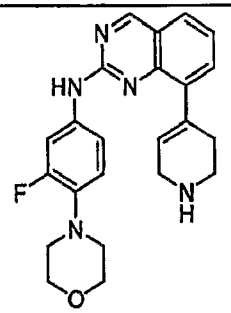
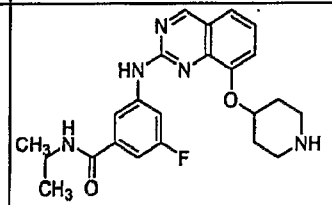
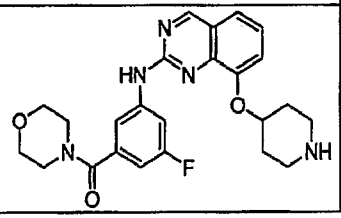
WO 2007/117607 PCT/US2007/008592

450		3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(trifluoromethyl)benzoic acid	433.1, 2.28	example 9 step 3 then example 8 step2	++++		+++	
451		ethyl 3-fluoro-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoate	411.1, 2.43	example 9 step 3 then example 8 step2	++++		++++	
452		N-(3-bromo-5-(trifluoromethyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	467.0/469, 2.62	example 9 step 3 then example 8 step2	++++		++++	
453		N-isopropyl-3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(trifluoromethyl)benzamide	474.2, 2.39		++++		++++	
454		morpholino(3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(trifluoromethyl)phenyl)methanone	502.2, 2.24		++++		+++	

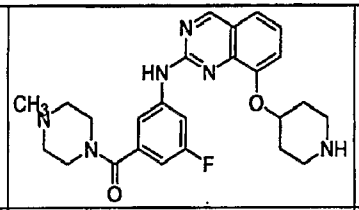
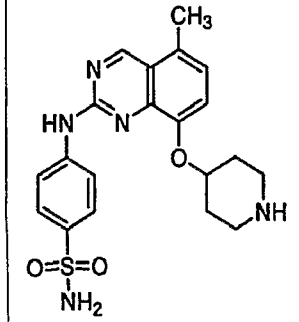
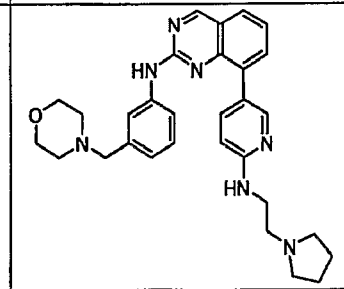
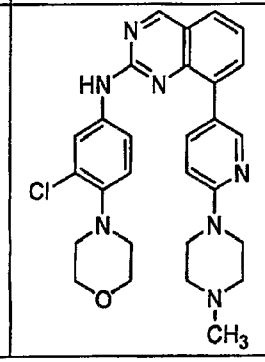
WO 2007/117607 PCT/US2007/008592

455		N,N-dimethyl-2-morpholino-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	477.2, 1.98		++++		+++	
456		N-cyclopropyl-2-morpholino-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	489.2, 2.00		++++		++++	
457		N-(3-fluoro-4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	424.2, 2.05	example 9 step 3 then example 8 step2	++++		++++	
458		N-(4-(oxazol-5-yl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	388.1, 2.08	example 9 step 3 then example 8 step2	++++		++++	

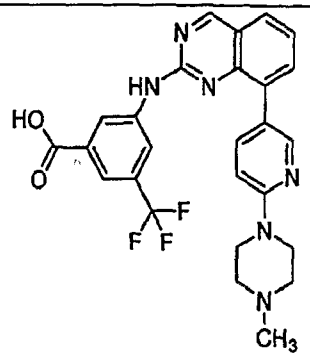
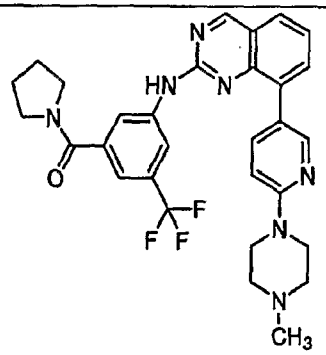
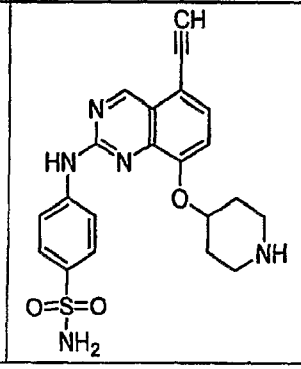
WO 2007/117607 PCT/US2007/008592

459		N-(3-fluoro-4-morpholinophenyl)-8-(4-(4-methylpiperazin-1-yl)phenyl)quinazolin-2-amine	499.2, 2.39	Suzuki (see example 8 step 1)	++++		++++	
460		N-(3-fluoro-4-morpholinophenyl)-8-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-2-amine	406.1, 2.09	Suzuki (see example 8 step 1)	++++		++++	
461		3-fluoro-N-isopropyl-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	424.2, 2.16		++++		++++	
462		(3-fluoro-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	452.1, 2.04		++++		++++	

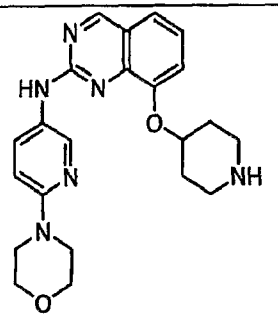
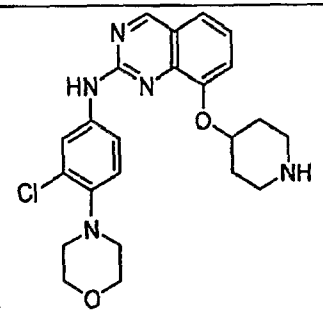
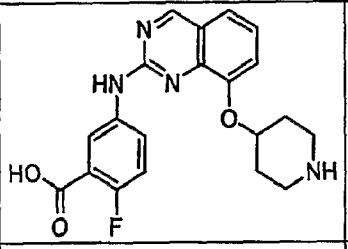
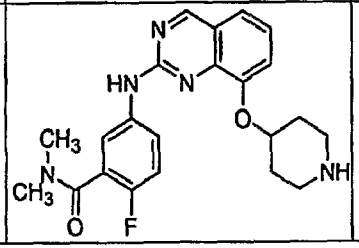
WO 2007/117607 PCT/US2007/008592

463		(3-fluoro-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(4-methylpiperazin-1-yl)methanone	465.2, 1.78		++++		++++	
464		4-(5-methyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	414.1, 1.97	example 105	++++		+++	
465		N-(3-(morpholinomethyl)phenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine	510.2, 1.78	Suzuki (see example 8 step 1)	++++		++++	
466		N-(3-chloro-4-morpholinophenyl)-8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-amine	516.1, 2.13	Suzuki (see example 8 step 1)	++++		++++	

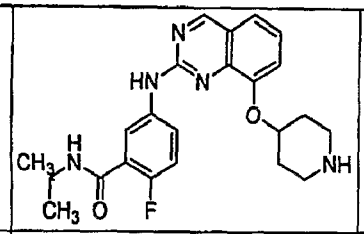
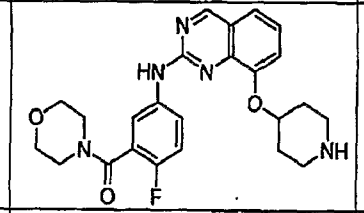
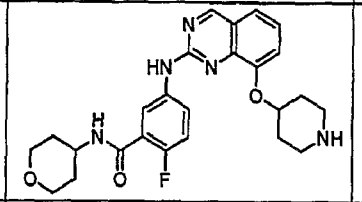
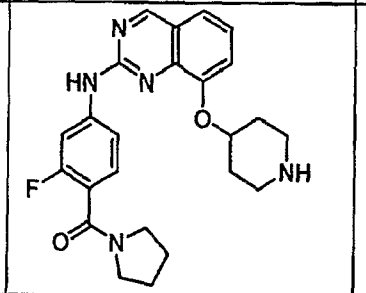
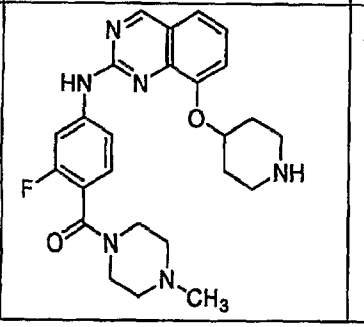
WO 2007/117607 PCT/US2007/008592

467		3-(8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)-5-(trifluoromethyl)benzoic acid	509.1, 2.14	Suzuki (see example 8 step 1)	++++		++++	
468		(3-(8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)-5-(trifluoromethyl)phenyl)(pyrrolidin-1-yl)methanone	562.2, 2.23		+++		++++	
469		4-(5-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	424.1, 2.06		++++		+++	

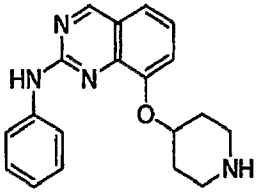
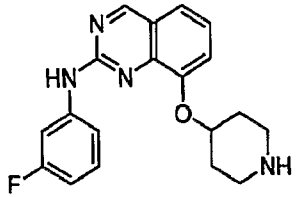
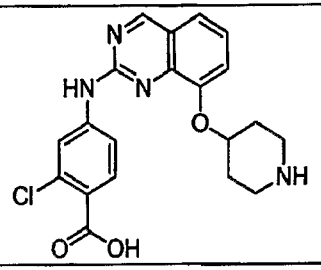
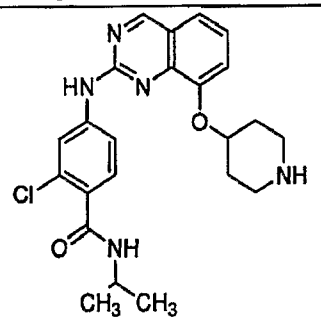
WO 2007/117607 PCT/US2007/008592

470		N-(6-morpholinopyridin-3-yl)-8-(piperidin-4-yloxy)quinazolin-2-amine	407.1, 1.69	example 9 step 3 then example 8 step2	++++		++++	
471		N-(3-chloro-4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	440.1, 2.18	example 9 step 3 then example 8 step2	++++		++++	
472		2-fluoro-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoic acid	383.1, 1.92	example 9 step 3 then example 8 step 2	++++		+++	
473		2-fluoro-N,N-dimethyl-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	410.1, 1.96		++++		++++	

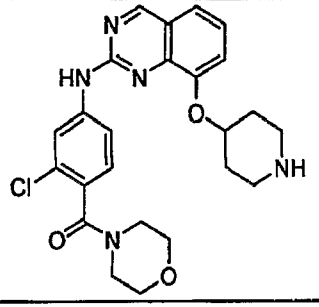
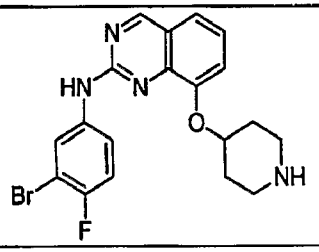
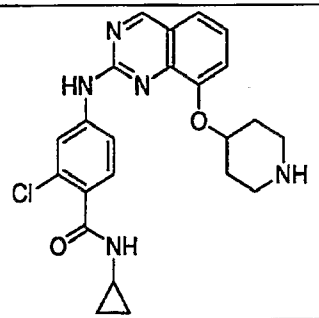
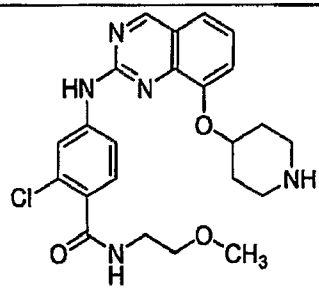
WO 2007/117607 PCT/US2007/008592

474		2-fluoro-N-isopropyl-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	424.2, 2.08		++++		++++	
475		(2-fluoro-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	452.1, 1.93		++++		+++	
476		2-fluoro-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(tetrahydro-2H-pyran-4-yl)benzamide	466.1, 1.92		++++		++++	
477		(2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(pyrrolidin-1-yl)methanone	436.1, 2.12		++++		++++	
478		(2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(4-methylpiperazin-1-yl)methanone	465.2, 1.71		++++		++++	

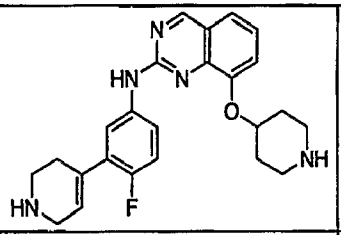
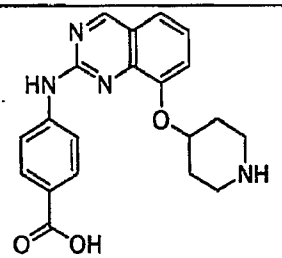
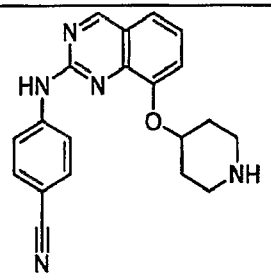
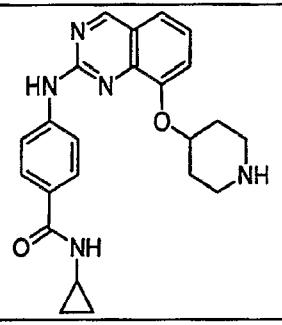
WO 2007/117607 PCT/US2007/008592

479		N-phenyl-8-(piperidin-4-yloxy)quinazolin-2-amine	321.1, 1.98	example 9 step 3 then example 8 step2	++++		++++	
480		N-(3-fluorophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	339.1, 2.13	example 9 step 3 then example 8 step2	++++		++++	
481		2-chloro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoic acid	399.1, 2.06	example 9 step 3 then example 8 step2	++++		+++	
482		2-chloro-N-isopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	440.1, 2.13		++++		++++	

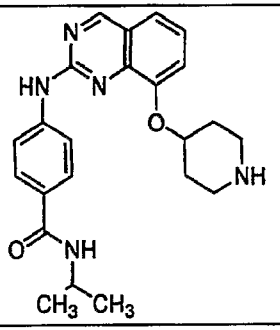
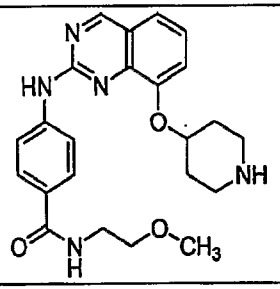
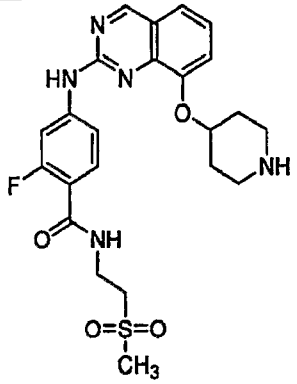
WO 2007/117607 PCT/US2007/008592

483		(2-chloro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	468.1, 2.02		++++		++++	
484		N-(3-bromo-4-fluorophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	417.0/419.0, 2.32	example 9 step 3 then example 8 step2	++++		++++	
485		2-chloro-N-cyclopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	438.1, 2.05		++++		++++	
486		2-chloro-N-(2-methoxyethyl)-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	456.1, 1.99		++++		++++	

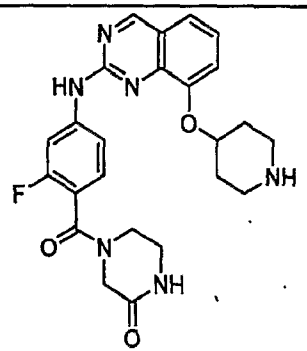
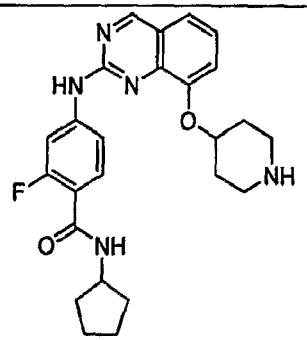
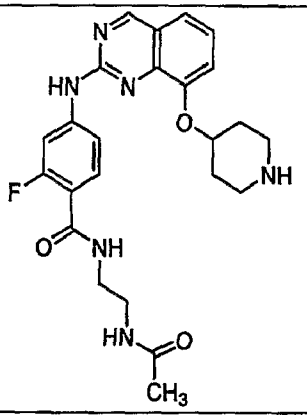
WO 2007/117607 PCT/US2007/008592

487		N-(4-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	420.2, 1.78	Suzuki (see example 8 step 1 and 2)	++++		++++	
488		4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoic acid	365.1, 1.95	example 9 step 3 then example 8 step2	++++		++++	
489		4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzonitrile	346.1, 2.13	example 9 step 3 then example 8 step2	++++		++++	
490		N-cyclopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	404.2, 1.95		++++		++++	

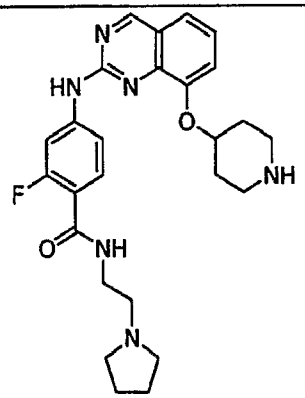
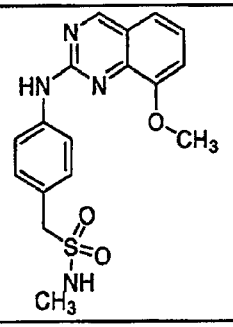
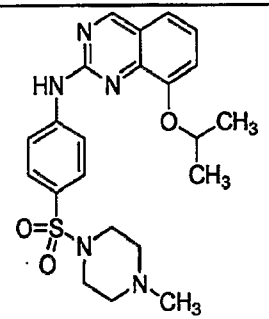
WO 2007/117607 PCT/US2007/008592

491		N-isopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	406.2, 2.03		++++		++++	
492		N-(2-methoxyethyl)-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	422.2, 1.91		++++		++++	
493		2-fluoro-N-(2-(methylsulfonyl)ethyl)-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	488.1, 1.95		++++		++++	

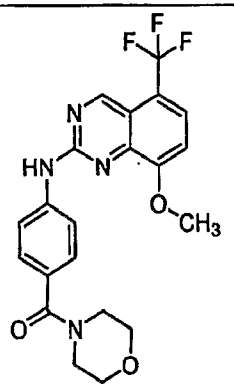
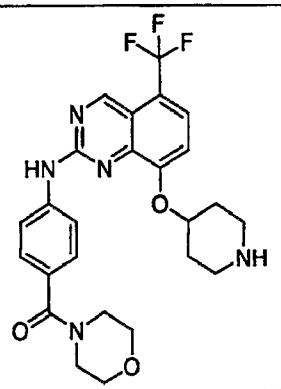
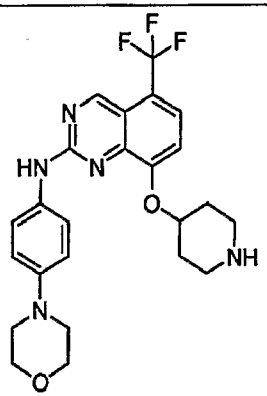
WO 2007/117607 PCT/US2007/008592

494		4-(2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzoyl)piperazin-2-one	465.2, 1.84		++++		+++	
495		N-cyclopentyl-2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	450.2, 2.32		++++		++++	
496		N-(2-acetamidoethyl)-2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	467.2, 1.89		++++		+++	

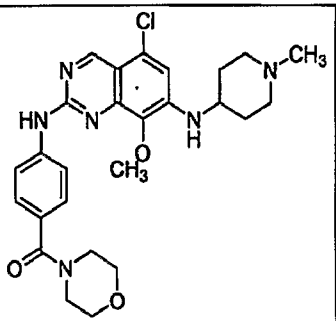
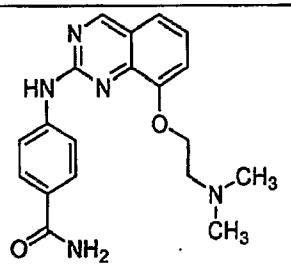
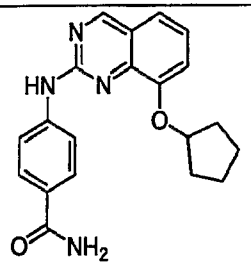
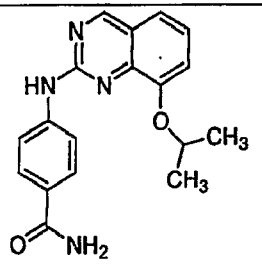
WO 2007/117607 PCT/US2007/008592

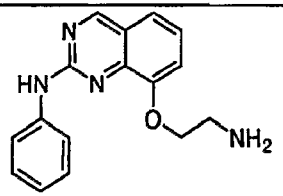
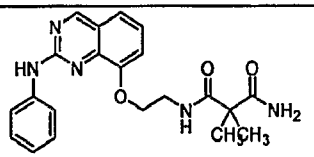
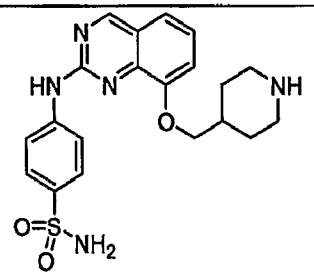
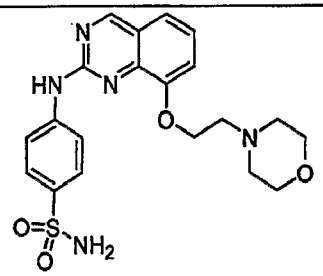
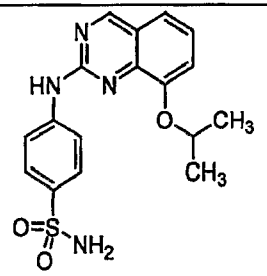
497		2-fluoro-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide	479.2, 1.83		++++		++++	
498		1-(4-(8-methoxyquinazolin-2-ylamino)phenyl)-N-methylmethanesulfonamide	359.1	Similar to example 2	++++	+++		
499		8-isopropoxy-N-(4-(4-methylpiperazin-1-ylsulfonyl)phenyl)quinazolin-2-amine	442.1	Similar to example 2	++++	+++		

WO 2007/117607 PCT/US2007/008592

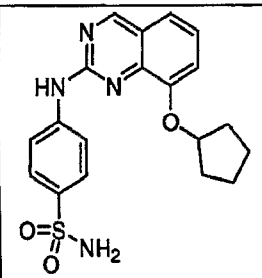
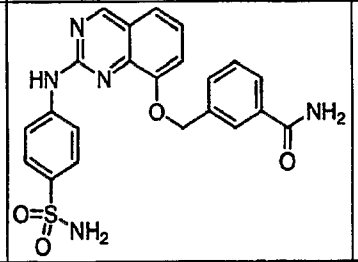
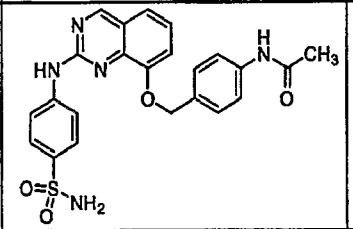
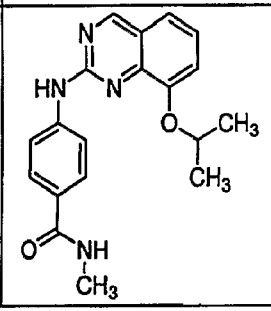
500		(4-(8-methoxy-5-(trifluoromethyl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	433.2, 2.59	Similar to example 51	++++		+++	
501		morpholino(4-(8-(piperidin-4-yloxy)-5-(trifluoromethyl)quinazolin-2-ylamino)phenyl)methanone	502.2, 2.29	Similar to example 52	++++		+++	
502		N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)-5-(trifluoromethyl)quinazolin-2-amine	474.2, 2.16	Similar to example 52	++++		++++	

WO 2007/117607 PCT/US2007/008592

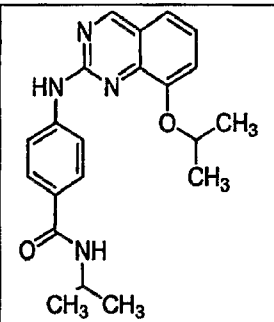
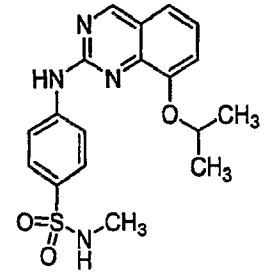
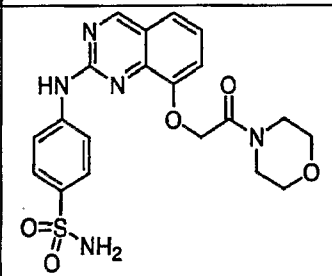
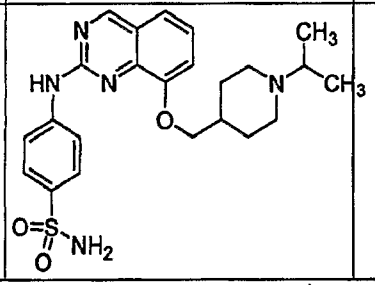
503		(4-(5-chloro-8-methoxy-7-(1-methylpiperidin-4-ylamino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	48.1, 2.1	Similar to example 34	++++		+++	
504		4-(8-(2-(dimethylamino)ethoxy)quinazolin-2-ylamino)benzamide	352.1, 1.70	Examples 1, using 4-aminobenzamide in place of sulfanilamide and N,N-dimethylethanolamine in place of 4-hydroxy-1-methylpiperidine	++++	++++		
505		4-(8-(cyclopentyloxy)quinazolin-2-ylamino)benzamide	349.1, 2.51	Examples 1, using 4-aminobenzamide in place of sulfanilamide and cyclopentanol in place of 4-hydroxy-1-methylpiperidine	++++	++++		
506		4-(8-isopropoxyquinazolin-2-ylamino)benzamide	2.25, 323.2	Examples 1, using 4-aminobenzamide in place of sulfanilamide and 2-propanol in place of 4-hydroxy-1-methylpiperidine	++++	++++		

507		8-(2-aminoethoxy)-N-phenylquinazolin-2-amine	281.1, 1.94	Similar to Example 14	++++	+++		
508		2,2-dimethyl-N1-(2-(2-(phenylamino)quinazolin-8-yloxy)ethyl)malonamide	394.2, 2.07	Similar to Example 15	+++	+++		
509		4-(8-(piperidin-4-ylmethoxy)quinazolin-2-ylamino)benzenesulfonamide	414.1, 1.90	Example 1, using 4-hydroxymethylpiperidine in place of 4-hydroxy-1-methylpiperidine	++++	++++	++++	
510		4-(8-(2-morpholinoethoxy)quinazolin-2-ylamino)benzenesulfonamide	430.1, 1.77	Example 1, using N-(2-hydroxyethyl)morpholine in place of 4-hydroxy-1-methylpiperidine	++++	++++		
511		4-(8-isopropoxyquinazolin-2-ylamino)benzenesulfonamide	359.1, 2.44	Example 1, using 2-propanol in place of 4-hydroxy-1-methylpiperidine	++++	++++	++++	

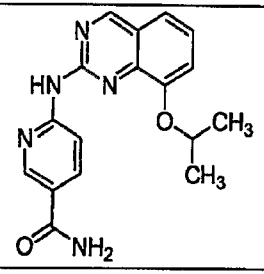
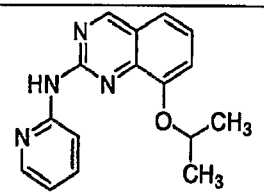
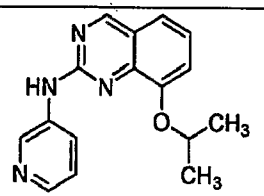
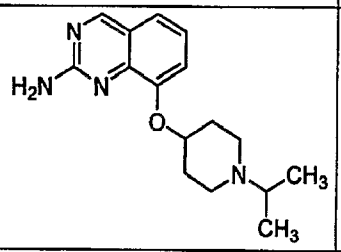
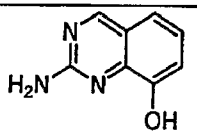
WO 2007/117607 PCT/US2007/008592

512		4-(8-(cyclopentyloxy)quinazolin-2-ylamino)benzenesulfonamide	385.1, 2.74	Example 1, using cyclopropanol in place of 4-hydroxy-1-methylpiperidine	++++	++++	++++	
513		3-((2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)methyl)benzamide	450.0, 2.24	Example 14 steps1 and 2, using 3-chloromethylbenzamide in place of N-(2-bromoethyl)phthalimide and sulfanilamide in place of aniline	++++	++++		
514		N-(4-((2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)methyl)phenyl)acetamide	464.1, 2.32	Example 14 steps1 and 2, using 4-acetamidobenzyl chloride in place of N-(2-bromoethyl)phthalimide and sulfanilamide in place of aniline	++++	++++		
515		4-(8-isopropoxyquinazolin-2-ylamino)-N-methylbenzamide	337.1, 2.33	Similar to Example 16	++++	++++		

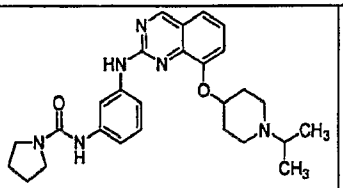
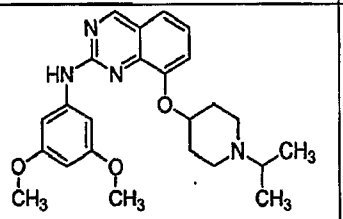
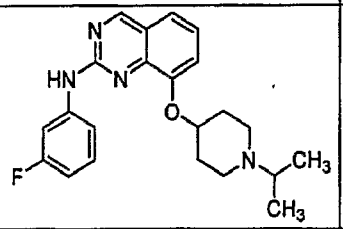
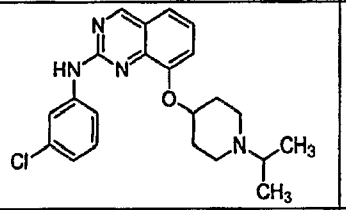
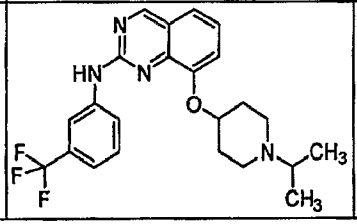
WO 2007/117607 PCT/US2007/008592

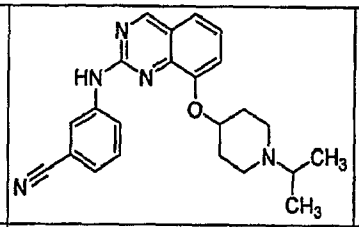
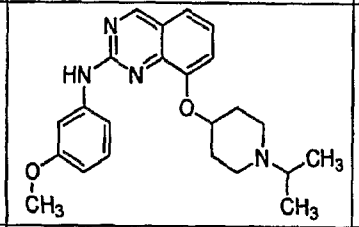
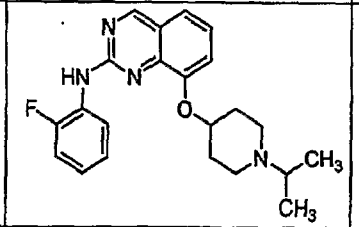
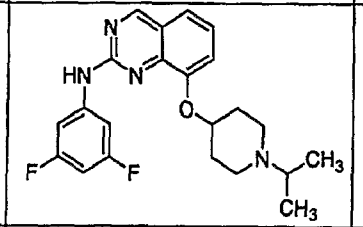
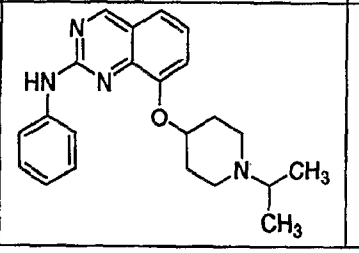
516		4-(8-isopropoxyquinazolin-2-ylamino)-N-isopropylbenzamide	365.1, 2.67	Example 16, using 4-amino-N-isopropylbenzamide in place of 4-amino-N-methylbenzamide	++++	++++		
517		4-(8-isopropoxyquinazolin-2-ylamino)-N-methylbenzenesulfonamide	373.1, 2.69	Example 16, using 4-amino-N-methylbenzenesulfonamide in place of 4-amino-N-methylbenzamide	++++	++++		
518		4-(8-(2-morpholino-2-oxoethoxy)quinazolin-2-ylamino)benzenesulfonamide	444.0, 1.96	Example 14 steps1 and 2, using 2-chloro-1-morpholinoethan-1-one in place of N-(2-bromoethyl)phthalimide and sulfanilamide in place of aniline	+++	+++		
519		4-(8-((1-isopropylpiperidin-4-yl)methoxy)quinazolin-2-ylamino)benzenesulfonamide	456.1, 2.00	Example 1, using 4-hydroxymethyl-N-isopropylpiperidine in place of 4-hydroxy-1-methylpiperidine	++++	++++	++++	

WO 2007/117607 PCT/US2007/008592

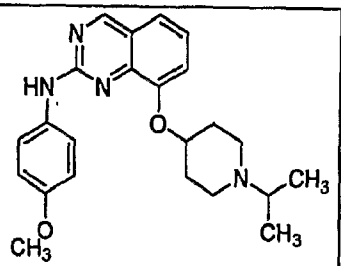
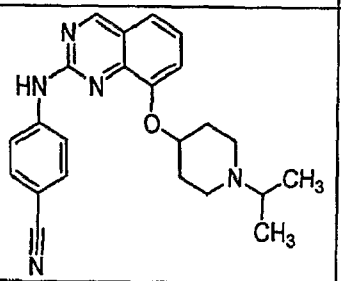
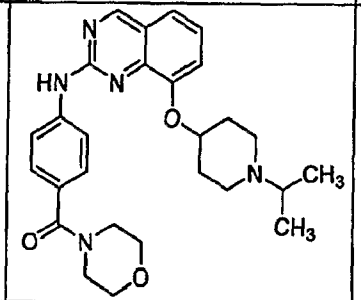
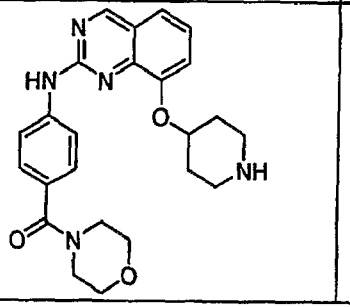
520		6-(8-isopropoxyquinazolin-2-ylamino)nicotinamide	324.1, 1.87	Similar to Example 16, using 2-aminonicotinamide in place of 4-amino-N-methylbenzamide	+	+++	++++	
521		8-isopropoxy-N-(pyridin-2-yl)quinazolin-2-amine	281.1, 2.09	Similar to Example 16, using 2-aminonicotinamide in place of 4-amino-N-methylbenzamide	+	+++	++++	
522		8-isopropoxy-N-(pyridin-3-yl)quinazolin-2-amine	281.1, 1.98	Similar to Example 16, using 3-aminopyridine in place of 4-amino-N-methylbenzamide	+	+++		
523		8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	287.2, 1.22	Similar to Example 19	+++		+++	
524		2-aminoquinazolin-8-ol	162.1, 0.70	Example 19, starting with 2-chloroquinazolin-8-ol in place of 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline	++		++++	

WO 2007/117607 PCT/US2007/008592

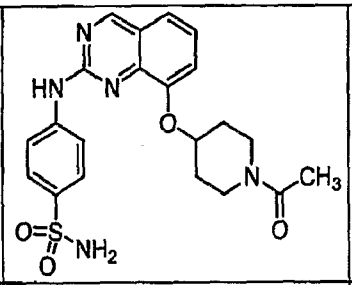
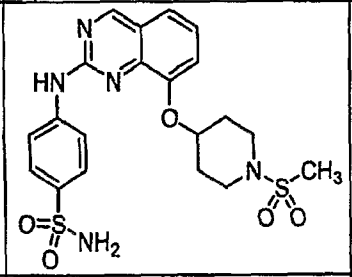
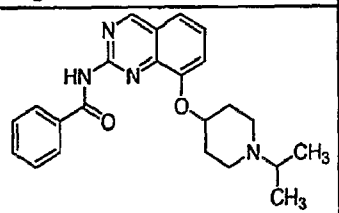
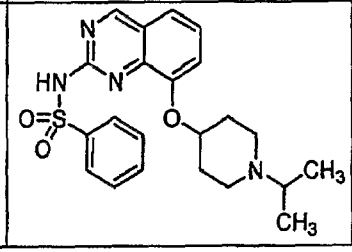
525		N-(3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)pyrrolidine-1-carboxamide	475.2, 2.02	Example 13, using 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in place of 2-chloro-8-methoxyquinazoline and N-(3-aminophenyl)pyrrolidine-1-carboxamide in place of 3,5-dimethoxyaniline	++++		++++	
526		N-(3,5-dimethoxyphenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	423.1, 2.29	Example 13, using 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in place of 2-chloro-8-methoxyquinazoline	++++		+++	
527		N-(3-fluorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	381.1, 2.29	Example 18 step 2, using 3-fluoroaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
528		N-(3-chlorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	397.1, 2.41	Example 18 step 2, using 3-chloroaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
529		8-(1-isopropylpiperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine	431.1, 2.52	Example 18 step 2, using 3-trifluoromethylaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	

530		3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzonitrile	388.1, 2.25	Example 18 step 2, using 3-aminobenzonitrile in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
531		8-(1-isopropylpiperidin-4-yloxy)-N-(3-methoxyphenyl)quinazolin-2-amine	393.1, 2.20	Example 18 step 2, using 3-methoxyaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		+++	
532		N-(2-fluorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	381.1, 2.24	Example 18 step 2, using 2-fluoroaniline in place of 2-(4-aminophenyl)-N-methylacetamide	+++		+++	
533		N-(3,5-difluorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	399.1, 2.41	Example 18 step 2, using 3,5-difluoroaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
534		8-(1-isopropylpiperidin-4-yloxy)-N-phenylquinazolin-2-amine	363.2, 2.13	Example 18 step 2, using aniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	

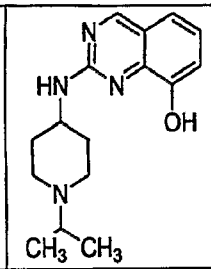
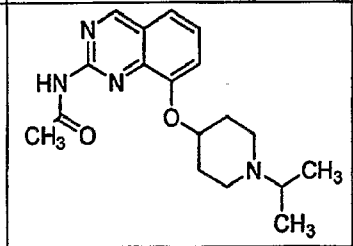
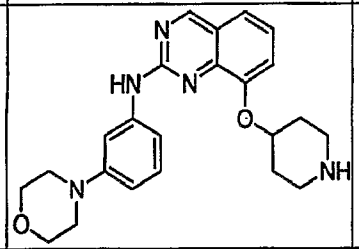
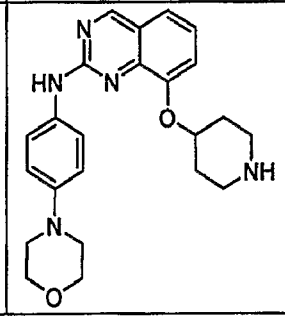
WO 2007/117607 PCT/US2007/008592

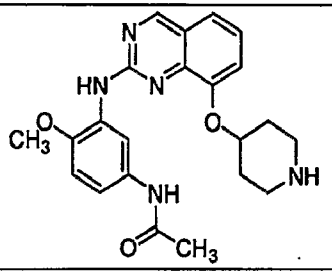
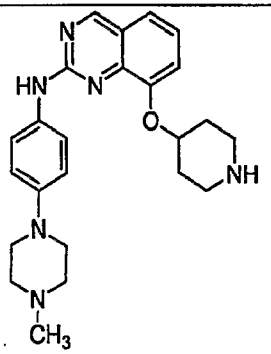
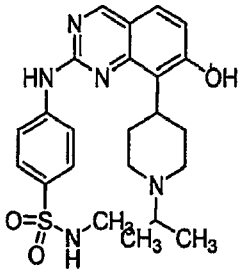
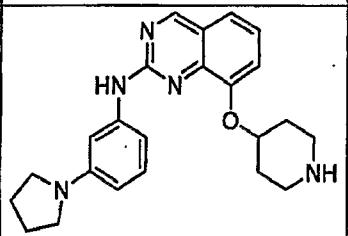
535		8-(1-isopropylpiperidin-4-yloxy)-N-(4-methoxyphenyl)quinazolin-2-amine	393.1, 2.06	Example 18 step 2, using 4-methoxyaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		+++	
536		4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzonitrile	388.1, 2.22	Example 18 step 2, using 4-aminobenzonitrile in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
537		(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	476.2, 1.99	Example 18 step 2, using (4-aminophenyl)(morpholino)methanone in place of 2-(4-aminophenyl)-N-methylacetamide	++++		+++	
538		morpholino(4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)methanone	434.1, 1.90	Similar to Example 20	++++		++++	

WO 2007/117607 PCT/US2007/008592

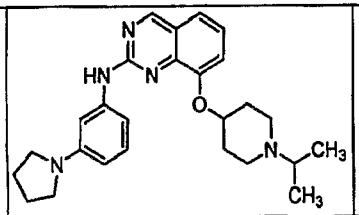
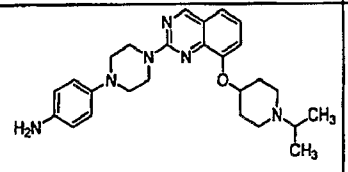
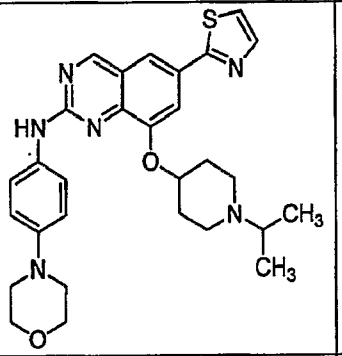
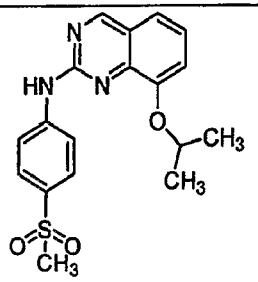
539		4-(8-(1-acetylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	442.0, 2.15	Similar to Example 21	++++		++++	
540		4-(8-(1-(methylsulfonyl)piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	478.0, 2.33	Similar to Example 21, using methanesulfonyl chloride in place of acetyl chloride	++++		++++	
541		N-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-yl)benzamide			+		+++	
542		N-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-yl)benzenesulfonamide			+		+++	

WO 2007/117607 PCT/US2007/008592

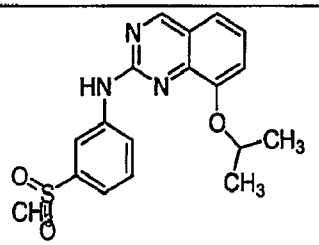
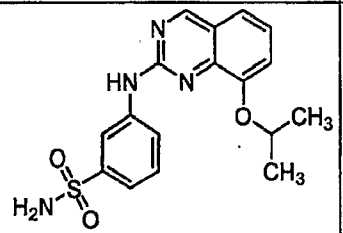
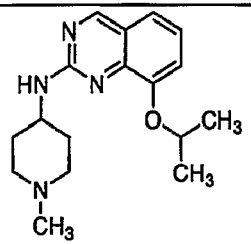
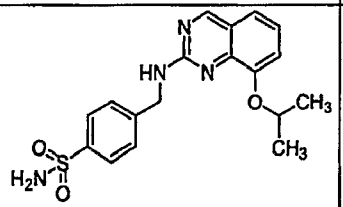
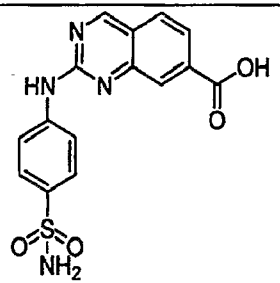
543		2-(1-isopropylpiperidin-4-ylamino)quinazolin-8-ol			+		+++	
544		N-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-yl)acetamide			+		+++	
545		N-(3-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	406.2, 1.87	Example 20 steps 2 and 3, using 3-morpholinoaniline in place of (4-aminophenyl)(morpholino)methanone	++++		++++	
546		N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	406.2, 1.82	Example 20 steps 2 and 3, using 4-morpholinoaniline in place of (4-aminophenyl)(morpholino)methanone	++++		++++	

547		N-(4-methoxy-3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide	408.1, 1.79	Example 20 steps 2 and 3, using 3-amino-4-methoxyacetanilide in place of (4-aminophenyl)(morpholino)methanone	+++		+++	
548		N-(4-(4-methylpiperazin-1-yl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	419.2, 1.61	Example 20 steps 2 and 3, using 3-amino-4-methoxyacetanilide in place of (4-aminophenyl)(morpholino)methanone	++++		++++	
549		4-(7-hydroxy-8-(1-isopropylpiperidin-4-yl)quinazolin-2-ylamino)-N-methylbenzenesulfonamide	456.1, 2.10	Example 1, using 3-(8-hydroxyquinazolin-2-ylamino)benzenesulfonamide and using methanol in place of 4-hydroxy-1-methylpiperidine	++++		++++	
550		8-(piperidin-4-yloxy)-N-(3-(pyrrolidin-1-yl)phenyl)quinazolin-2-amine	390.1, 1.85	Example 20 steps 2 and 3, using 3-pyrrolidin-1-ylaniline in place of (4-aminophenyl)(morpholino)methanone	++++		+++	

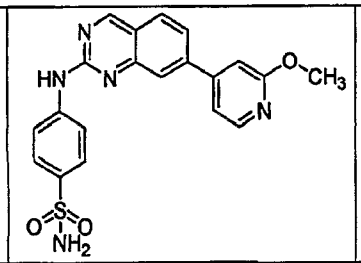
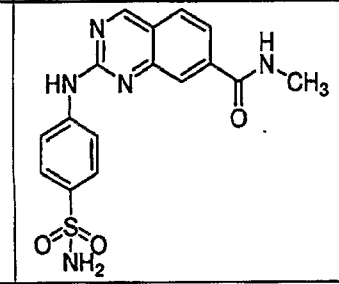
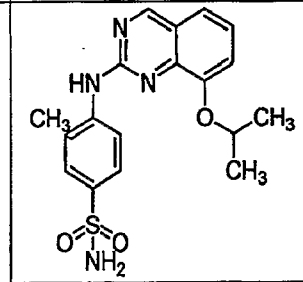
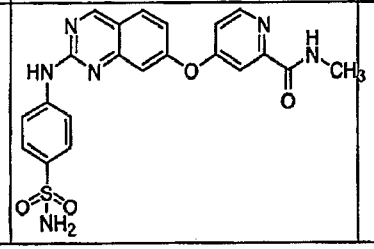
WO 2007/117607 PCT/US2007/008592

551		8-(1-isopropylpiperidin-4-yloxy)-N-(3-(pyrrolidin-1-yl)phenyl)quinazolin-2-amine	432.1, 2.10	Example 18 step 2, using 3-pyrrolidin-1-ylaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		+++	
552		4-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-yl)piperazin-1-yl)aniline	447.1, 1.80	Example 18 step 2, using 4-(4-methylpiperazin-1-yl)phenylamine in place of 2-(4-aminophenyl)-N-methylacetamide	++		+++	
553		8-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	531.2, 2.12	Example 22 step 1 using 4-morpholinoaniline in place of 3-morpholinoaniline then 214 step 2	++++		++++	
554		8-isopropoxy-N-(4-(methylsulfonyl)phenyl)quinazolin-2-amine	358.1, 3.59	Example 2	++++	++++		

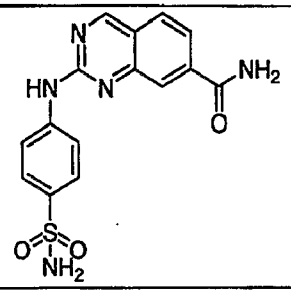
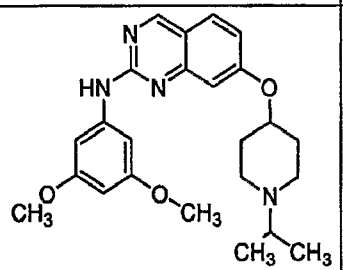
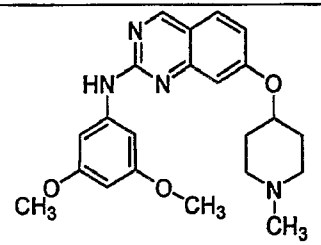
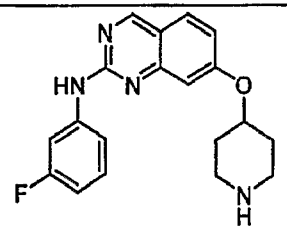
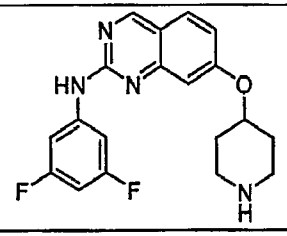
WO 2007/117607 PCT/US2007/008592

555		8-isopropoxy-N-(3-(methylsulfonyl)phenyl)quinazolin-2-amine	358.1, 3.47	Example 2	++++	++++		
556		3-(8-isopropoxyquinazolin-2-ylamino)benzenesulfonamide	359.1, 2.72	Example 2	++++	++++		
557		8-isopropoxy-N-(1-methylpiperidin-4-yl)quinazolin-2-amine	301.1, 1.8	Example 2	+	+++		
558		4-((8-isopropoxyquinazolin-2-ylamino)methyl)benzenesulfonamide	373.1, 2.31	Example 2	+	+++		
559		2-(4-sulfamoylphenylamino)quinazoline-7-carboxylic acid	345, 2.32	Example 29 Steps 1 to 6	++++	+++		

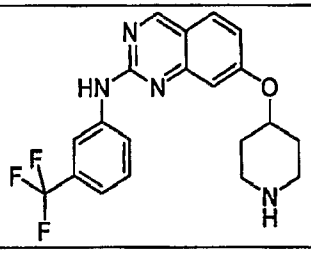
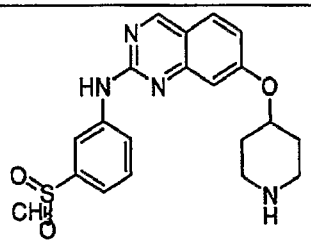
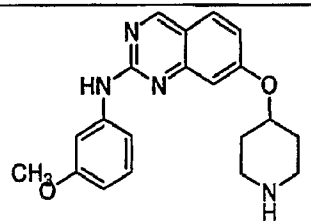
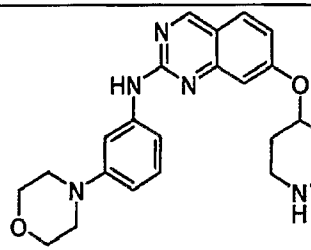
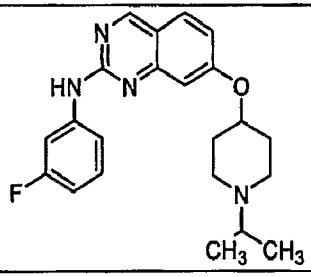
WO 2007/117607 PCT/US2007/008592

560		4-(7-(2-methoxypyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide	408, 2.94	Example 29 Step 1 to 2	+	+++		
561		N-methyl-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide	358, 2.0	Example 29 Steps 1 to 6	++++	++++		
562		4-(8-isopropoxyquinazolin-2-ylamino)-3-methylbenzenesulfonamide	373.1, 2.83	Example 2	++	++++		
563		N-methyl-4-(2-(4-sulfamoylphenylamino)quinazolin-7-yloxy)picolinamide	451.1, 2.22	Example 29	+	+++		

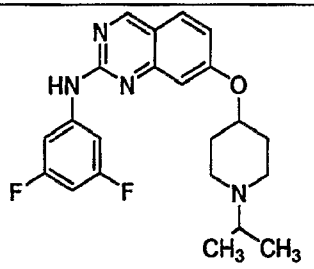
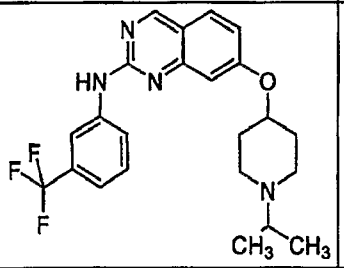
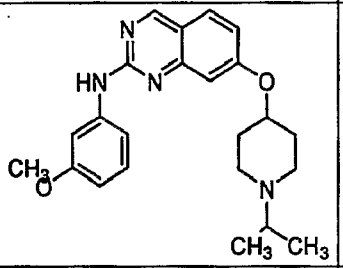
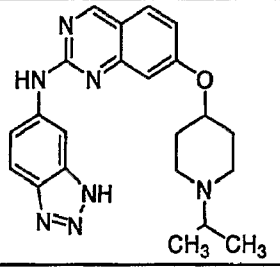
WO 2007/117607 PCT/US2007/008592

564		2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide	344, 1.85	Example 29 Steps 1 to 6	++++	++++		
565		N-(3,5-dimethoxyphenyl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	423.2, 2.4	Example 42 and Example 31	+++		+++	
566		N-(3,5-dimethoxyphenyl)-7-(1-methylpiperidin-4-yloxy)quinazolin-2-amine	395.2, 2.34	Example 42 and Example 32	++++		++++	
567		N-(3-fluorophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	339.1, 2.4	Example 42 and Example 32	++++		++++	
568		N-(3,5-difluorophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	357.1, 2.4	Example 42 and Example 32	++++		++++	

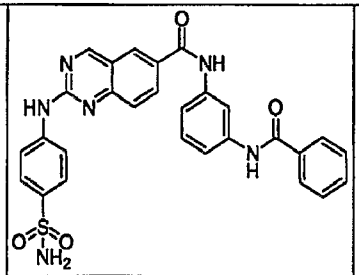
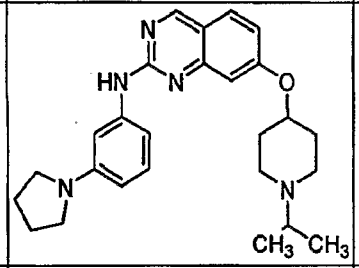
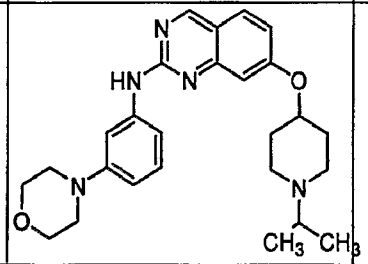
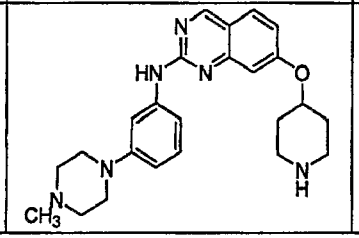
WO 2007/117607 PCT/US2007/008592

569		7-(piperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine	389.1, 2.81	Example 42 and Example 32	++++		++++	
570		N-(3-(methylsulfonyl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	399.1, 2.0	Example 42 and Example 32	++++		++++	
571		N-(3-methoxyphenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	351.1 2.1	Example 42 and Example 32	++++		++++	
572		N-(3-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	406.1, 1.9	Example 42 and Example 32	++++		++++	
573		N-(3-fluorophenyl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	381.1, 2.62	Example 42 and Example 32	++++		+++	

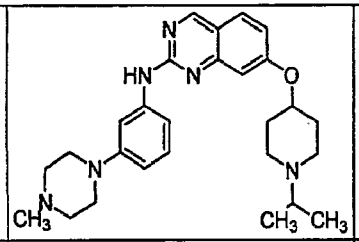
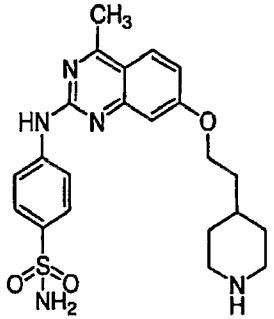
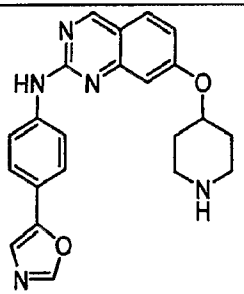
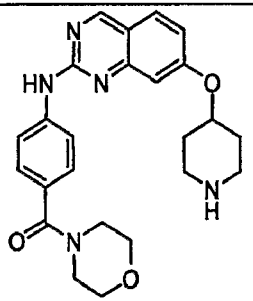
WO 2007/117607 PCT/US2007/008592

574		N-(3,5-difluorophenyl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	399.1, 3.0	Example 42 and Example 32	++++		++++	
575		7-(1-isopropylpiperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine	431.1, 3.1	Example 42 and Example 32	++++		++++	
576		7-(1-isopropylpiperidin-4-yloxy)-N-(3-methoxyphenyl)quinazolin-2-amine	393.2, 2.3	Example 42 and Example 32	++++		+++	
577		N-(1H-benzo[d][1,2,3]triazol-6-yl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine	404.1, 1.83	Example 42 and Example 32	++++		+++	

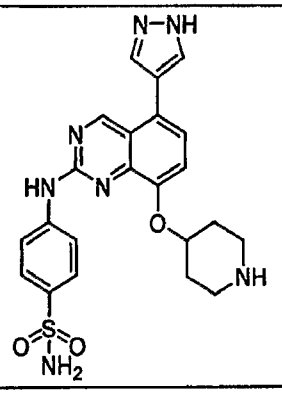
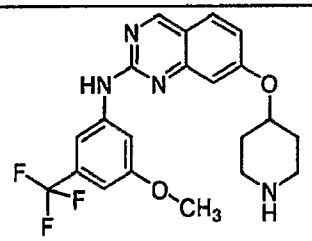
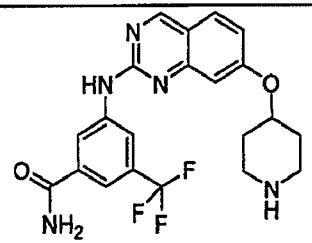
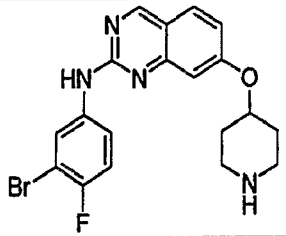
WO 2007/117607 PCT/US2007/008592

578		N-(3-benzamidophenyl)-2-(4-sulfamoylphenylamino)quinazoline-6-carboxamide	539.1, 3.42		+		++++	
579		7-(1-isopropylpiperidin-4-yloxy)-N-(3-(pyrrolidin-1-yl)phenyl)quinazolin-2-amine	432.2, 2.23	Example 42 and Example 32	++++		+++	
580		7-(1-isopropylpiperidin-4-yloxy)-N-(3-morpholinophenyl)quinazolin-2-amine	448.2, 2.0	Example 42 and Example 32	+++		+++	
581		N-(3-(4-methylpiperazin-1-yl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	419.2, 1.56	Example 42 and Example 32	++++		++++	

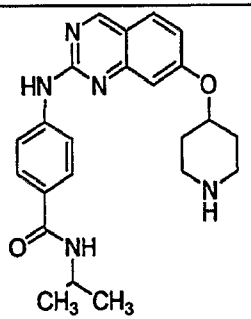
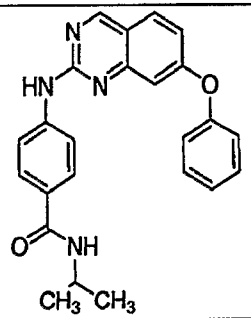
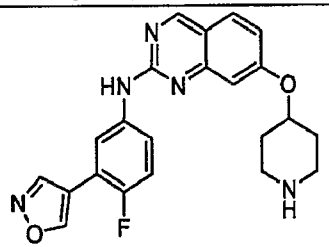
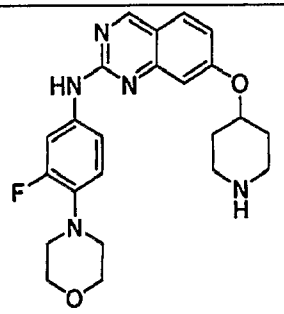
WO 2007/117607 PCT/US2007/008592

582		7-(1-isopropylpiperidin-4-yloxy)-N-(3-(4-methylpiperazin-1-yl)phenyl)quinazolin-2-amine	461.3, 1.7	Example 42 and Example 32	++++		+++	
583		4-(4-methyl-7-(2-(piperidin-4-yl)ethoxy)quinazolin-2-ylamino)benzenesulfonamide	442.2, 2.03	Example 33 Steps 1 to 6	++		+++	
584		N-(4-(oxazol-5-yl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	388.1, 2.2	Example 42 and Example 32	++++		++++	
585		morpholino(4-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)methanone	434.2/1.8	Example 42 and Example 32	++++		++++	

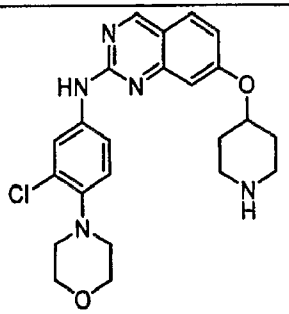
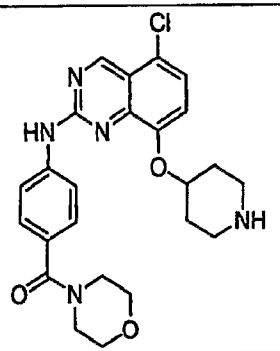
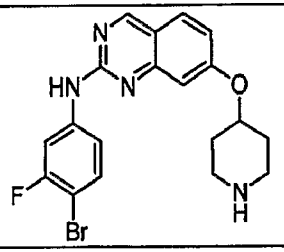
WO 2007/117607 PCT/US2007/008592

586		4-(8-(piperidin-4-yloxy)-5-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide	466.1, 1.7	Example 32 Steps 1 to 4	+++		+++	
587		N-(3-methoxy-5-(trifluoromethyl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	419.1, 2.91	Example 42 and Example 32	++++		++++	
588		3-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(trifluoromethyl)benzamide	432.2, 2.3	Example 42 and Example 32	++++		++++	
589		N-(3-bromo-4-fluorophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	419.1, 2.61	Example 42 and Example 32	++++		++++	

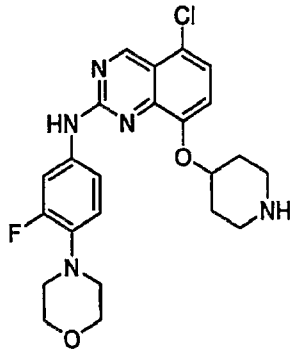
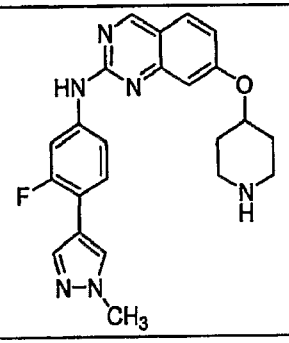
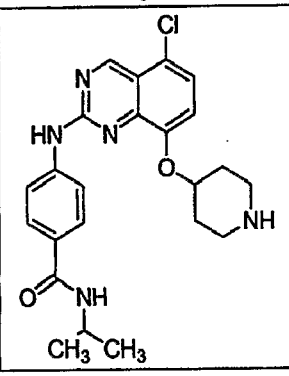
WO 2007/117607 PCT/US2007/008592

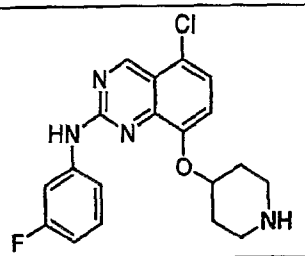
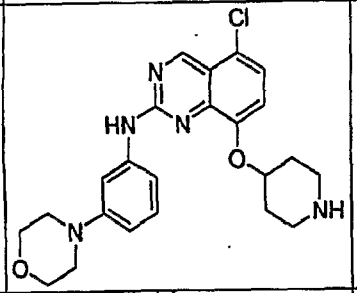
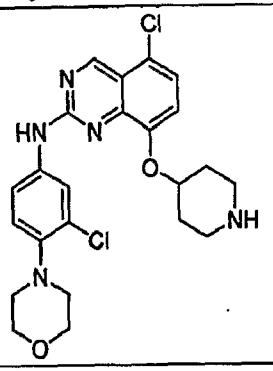
590		N-isopropyl-4-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide	406.2, 2.02	Example 42 and Example 32	++++		++++	
591		N-isopropyl-4-(7-phenoxyquinazolin-2-ylamino)benzamide	399.1, 3.9	Example 58	+		++++	
592		N-(4-fluoro-3-(isoxazol-4-yl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	406.1, 2.5	Example 42 and Example 32	++++		+++	
593		N-(3-fluoro-4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	424.2, 2.1	Example 42 and Example.32	++++		++++	

WO 2007/117607 PCT/US2007/008592

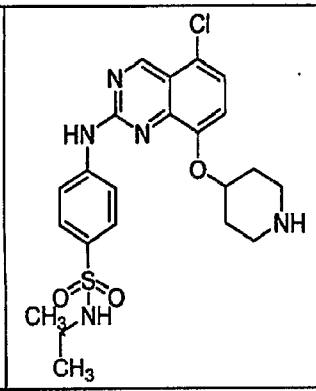
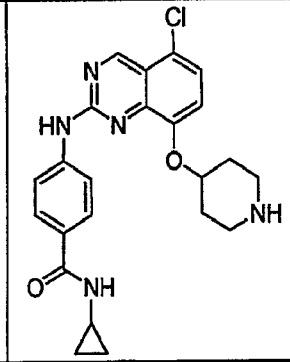
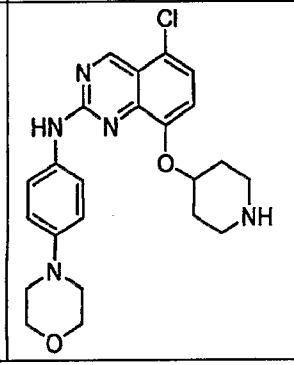
594		N-(3-chloro-4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	440.1, 2.4	Example 42 and Example 32	++++		++++	
595		(4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	468.1, 2.53	Example 32 Steps 1 to 4	++++		+++	
596		N-(4-bromo-3-fluorophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	419.1, 2.9	Example 42 and Example 32	++++		++++	

WO 2007/117607 PCT/US2007/008592

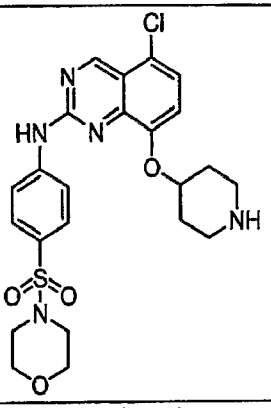
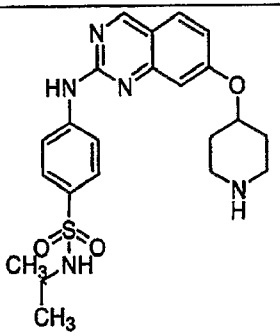
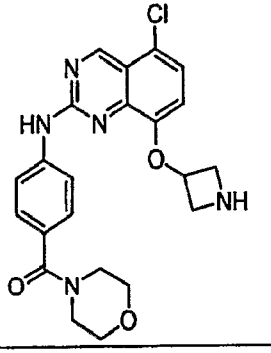
597		5-chloro-N-(3-fluoro-4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	458.1, 2.75	Example 32 Steps 1 to 4	++++		+++	
598		N-(3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	417, 2.0	Example 42 and Example 32	++++		+++	
599		4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzamide	440.2, 2.73	Example 32 Steps 1 to 4	++++		++++	

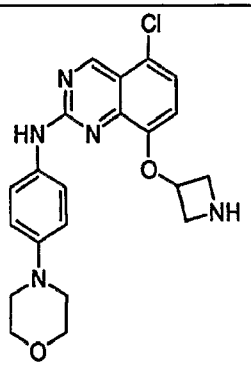
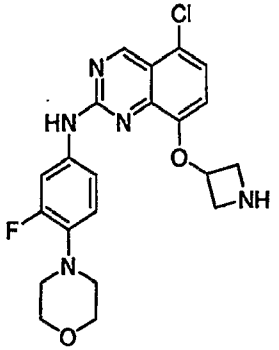
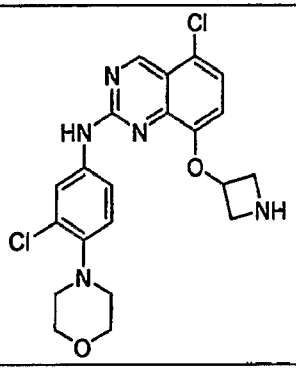
600		5-chloro-N-(3-fluorophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	373.1, 2.95	Example 32 Steps 1 to 4	++++		++++	
601		5-chloro-N-(3-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	440.1, 2.4	Example 32 Steps 1 to 4	++++		+++	
602		5-chloro-N-(3-chloro-4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	474.1, 2.96	Example 32 Steps 1 to 4	++++		++++	

WO 2007/117607 PCT/US2007/008592

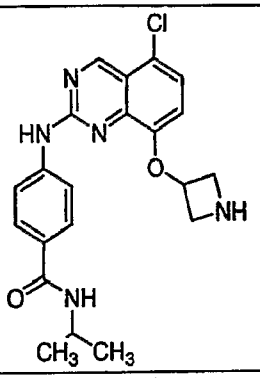
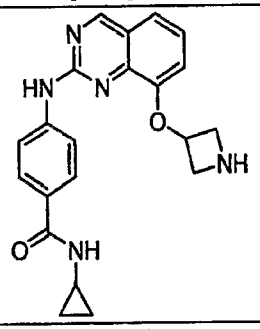
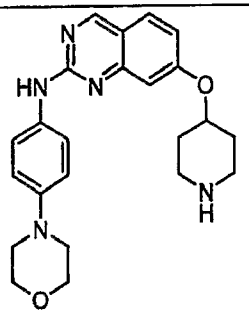
603		4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzenesulfonamide	476.1, 2.82	Example 32 Steps 1 to 4	++++		++++	
604		4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-cyclopropylbenzamide	438.1, 2.6	Example 32 Steps 1 to 4	++++		++++	
605		5-chloro-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	440.1, 2.1	Example 32 Steps 1 to 4	++++		+++	

WO 2007/117607 PCT/US2007/008592

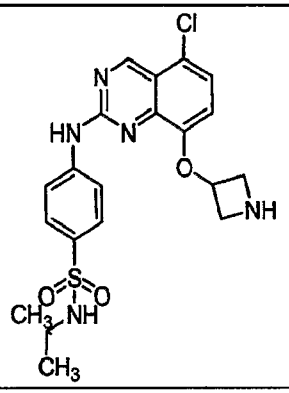
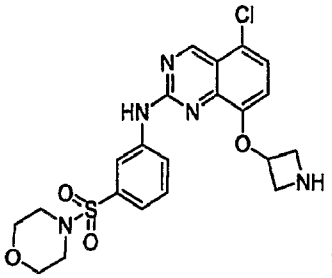
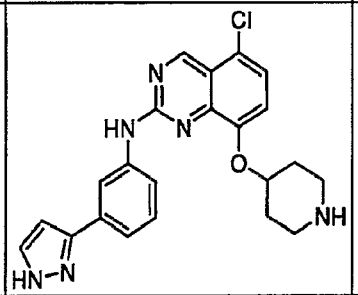
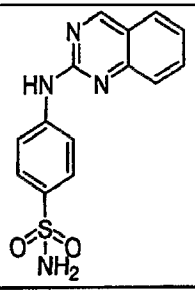
606		5-chloro-N-(4-(morpholinosulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	504, 2.8	Example 32 Steps 1 to 4	++++		++++	
607		N-isopropyl-4-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	442, 2.1	Example 32 Steps 1 to 4	++++		++++	
608		(4-(8-(azetidin-3-yloxy)-5-chloroquinazolin-2-ylamino)phenyl)(morpholino)methanone	440.2, 2.4	Example 32 Steps 1 to 4	++++		+++	

609		8-(azetidin-3-yloxy)-5-chloro-N-(4-morpholinophenyl)quinazolin-2-amine	412.1, 2.01	Example 32 Steps 1 to 4	++++		+++	
610		8-(azetidin-3-yloxy)-5-chloro-N-(3-fluoro-4-morpholinophenyl)quinazolin-2-amine	430.1, 2.54	Example 32 Steps 1 to 4	++++		+++	
611		8-(azetidin-3-yloxy)-5-chloro-N-(3-chloro-4-morpholinophenyl)quinazolin-2-amine	446.1, 2.9	Example 32 Steps 1 to 4	++++		++++	

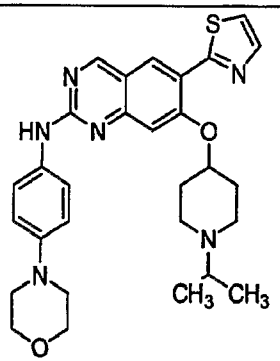
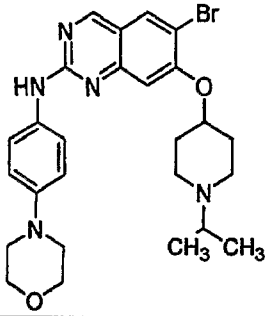
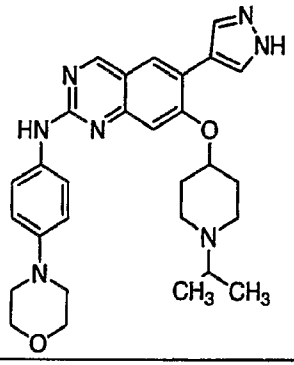
WO 2007/117607 PCT/US2007/008592

612		4-(8-(azetidin-3-yloxy)-5-chloroquinazolin-2-ylamino)-N-isopropylbenzamide	412.2, 2.49	Example 32 Steps 1 to 4	++++		+++	
613		4-(8-(azetidin-3-yloxy)-5-chloroquinazolin-2-ylamino)-N-cyclopropylbenzamide	410.1, 2.4	Example 32 Steps 1 to 4	++++		++++	
614		N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	406.2, 1.7	Example 42 and Example 32	++++		++++	

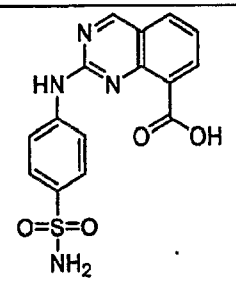
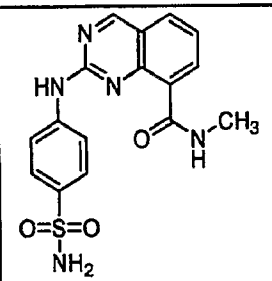
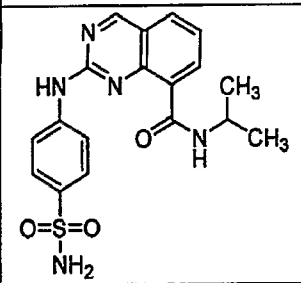
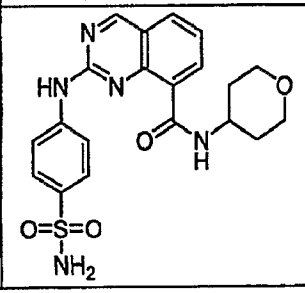
WO 2007/117607 PCT/US2007/008592

615		4-(8-(azetidin-3-yloxy)-5-chloroquinazolin-2-ylamino)-N-isopropylbenzenesulfonamide	448.1, 2.72	Example 32 Steps 1 to 4	++++		++++	
616		8-(azetidin-3-yloxy)-5-chloro-N-(3-(morpholinosulfonyl)phenyl)quinazolin-2-amine	476.1, 2.6	Example 32 Steps 1 to 4	++++		++++	
617		N-(3-(1H-pyrazol-3-yl)phenyl)-5-chloro-8-(piperidin-4-yloxy)quinazolin-2-amine	421.2, 2.7	Example 32 Steps 1 to 4	++++		+++	
618		4-(quinazolin-2-ylamino)benzenesulfonamide	301.1, 2.53	Example 36	++++		+++	

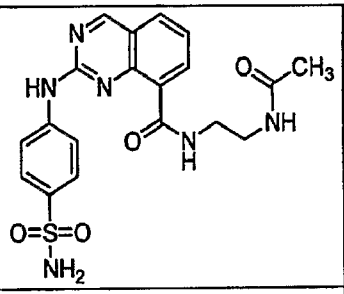
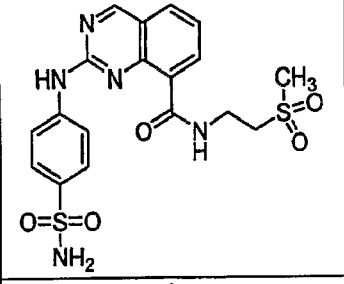
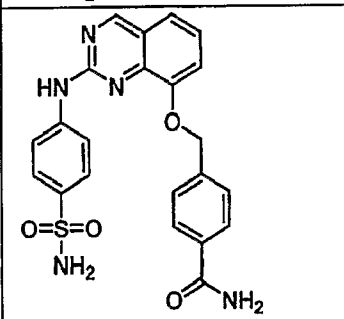
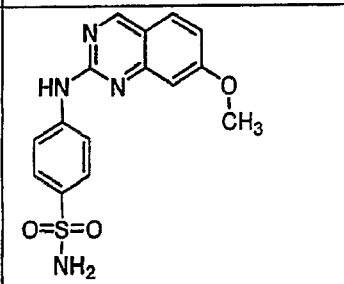
WO 2007/117607 PCT/US2007/008592

619		7-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	531.2, 2.2		++++		++++	
620		6-bromo-7-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)quinazolin-2-amine	526.2, 2.20		++++		++++	
621		7-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)-6-(1H-pyrazol-4-yl)quinazolin-2-amine	514.3, 1.9		++++		++++	

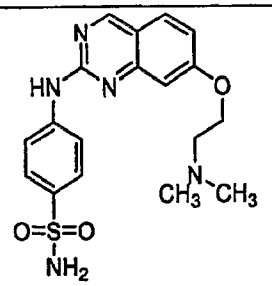
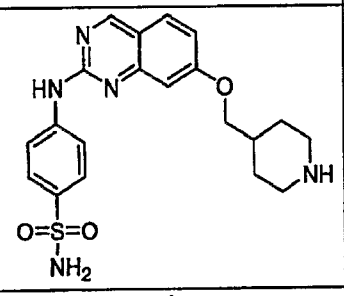
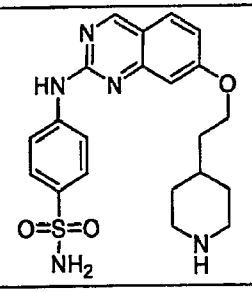
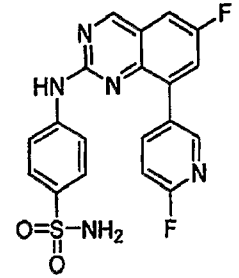
WO 2007/117607 PCT/US2007/008592

622		2-(4-sulfamoylphenylamino)quinazoline-8-carboxylic acid			+++	+++		
623		N-methyl-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			+	++++		
624		N-isopropyl-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			++++	++++		
625		2-(4-sulfamoylphenylamino)-N-(tetrahydro-2H-pyran-4-yl)quinazoline-8-carboxamide			+	++++		

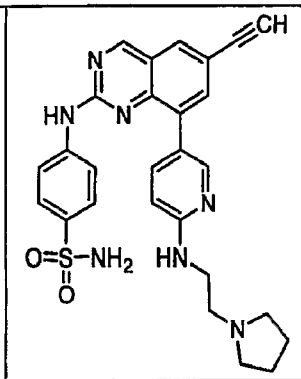
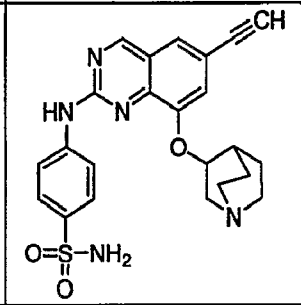
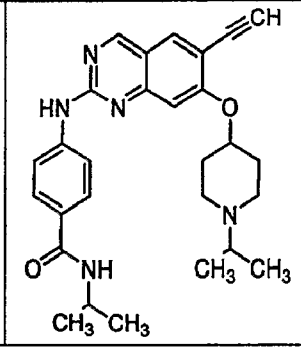
WO 2007/117607 PCT/US2007/008592

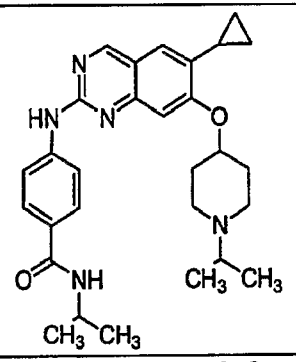
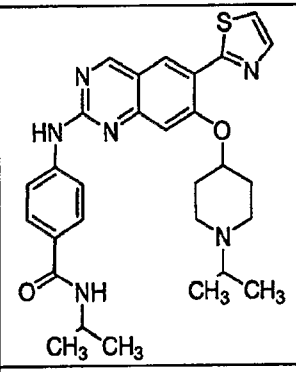
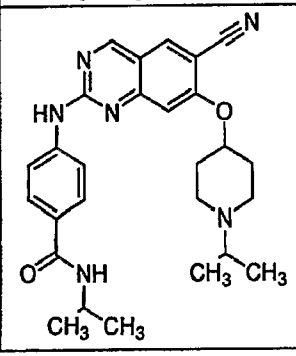
626		N-(2-acetamidoethyl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			+	+++		
627		N-(2-(methylsulfonyl)ethyl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			+	+++		
628		4-((2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)methyl)benzamide	450, 3.64	Similar to Example 1	++++	+++		
629		4-(7-methoxyquinazolin-2-ylamino)benzenesulfonamide	331, 2.51	Similar to Example 4	++++	++++		

WO 2007/117607 PCT/US2007/008592

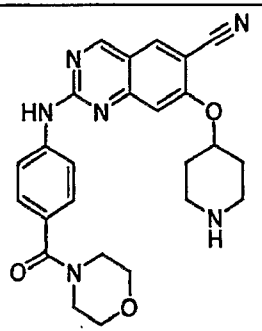
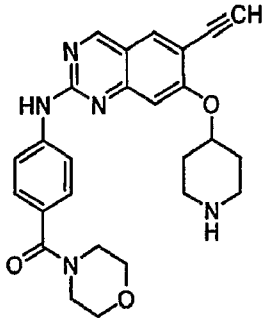
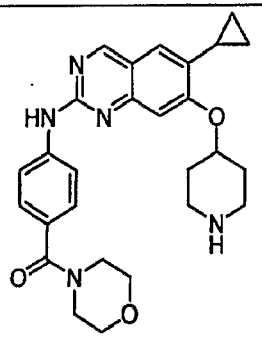
630		4-(7-(2-(dimethylamino)ethoxy)quinazolin-2-ylamino)benzenesulfonamide	388, 1.76	Similar to Example 4	++++	+++		
631		4-(7-(piperidin-4-ylmethoxy)quinazolin-2-ylamino)benzenesulfonamide	414, 2.58	Similar to Example 4	++++	++++		
632		4-(7-(2-(piperidin-4-yl)ethoxy)quinazolin-2-ylamino)benzenesulfonamide	428, 2.75	Similar to Example 4	++++	++++		
633		4-(6-fluoro-8-(6-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide	414, 4.38	Similar to Example 24	+	+++		

WO 2007/117607 PCT/US2007/008592

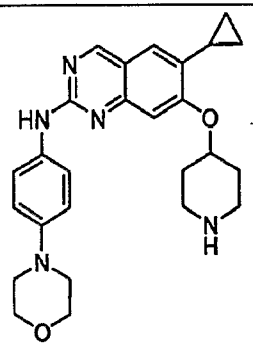
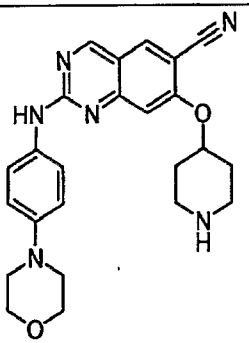
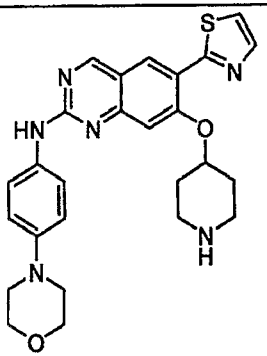
634		4-(6-ethynyl-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide	514, 2.18	Example 24 followed by SNAR reaction	++++		++++	
635		4-(6-ethynyl-8-(quinuclidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide	450, 2.39	Similar to Example 9	++++		++++	
636		4-(6-ethynyl-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzamide	472, 2.65	Example 27	++++		++++	

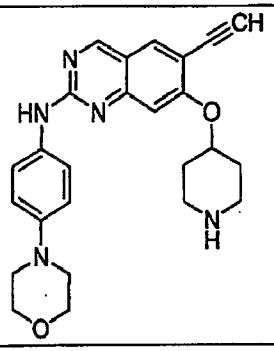
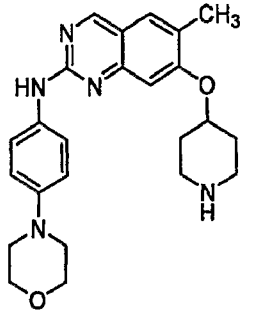
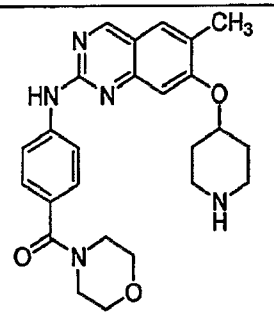
637		4-(6-cyclopropyl-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzamide	488, 2.64	Example 27	++++		++++	
638		N-isopropyl-4-(7-(1-isopropylpiperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide	531, 2.60	Example 27	++++		++++	
639		4-(6-cyclopropyl-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)-N-isopropylbenzamide	473, 2.53	Example 27	++++		++++	

WO 2007/117607 PCT/US2007/008592

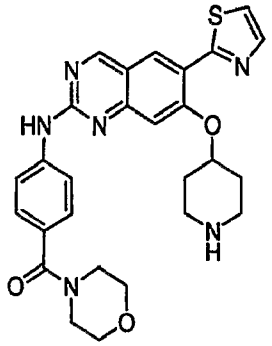
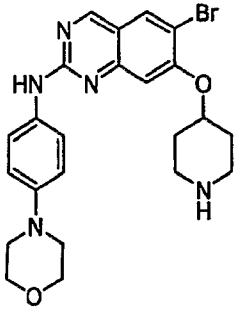
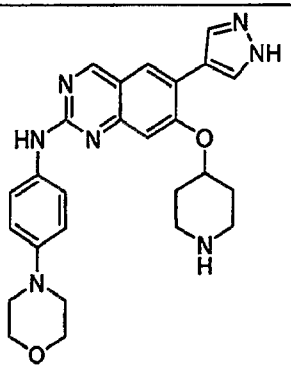
640		2-(4-(morpholine-4-carbonyl)phenylamino)-7-(piperidin-4-yloxy)quinazoline-6-carbonitrile	459, 2.11	Example 27	++++		++++	
641		(4-(6-ethynyl-7-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	458, 2.18	Example 27	++++		++++	
642		(4-(6-cyclopropyl-7-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	474, 2.24	Example 27	++++		++++	

WO 2007/117607 PCT/US2007/008592

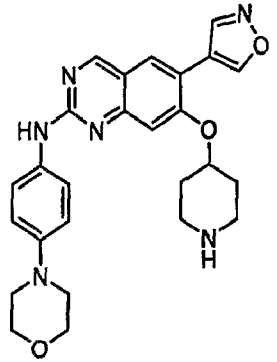
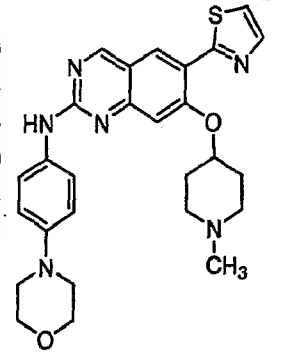
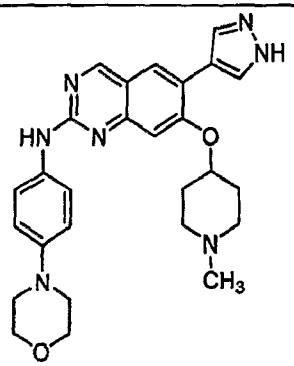
643		6-cyclopropyl-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	446, 2.12	Example 27	++++		++++	
644		2-(4-morpholinophenylamino)-7-(piperidin-4-yloxy)quinazoline-6-carbonitrile	431, 1.84	Example 27	++++		++++	
645		N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	489, 2.05	Example 27	++++	++++	++++	

646		6-ethynyl-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	430, 2.04	Example 27	++++	++++	++++	
647		6-methyl-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	420, 1.91	Example 27	++++	++++	++++	
648		(4-(6-methyl-7-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	448, 1.96	Example 27	++++	++++	++++	

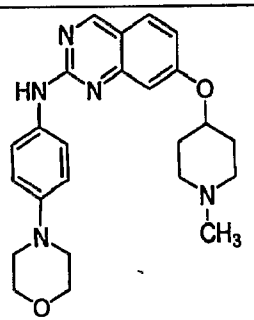
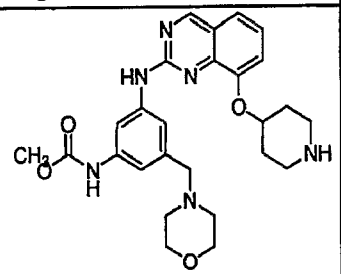
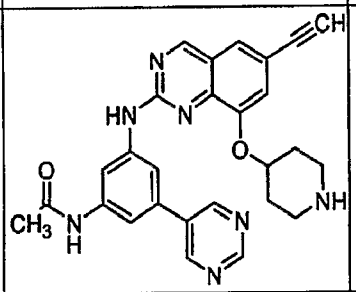
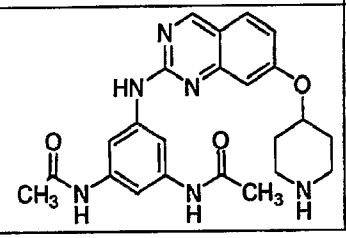
WO 2007/117607 PCT/US2007/008592

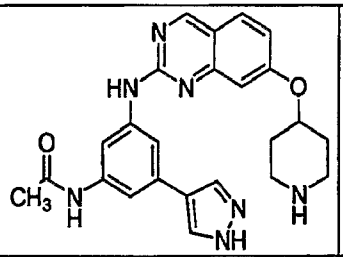
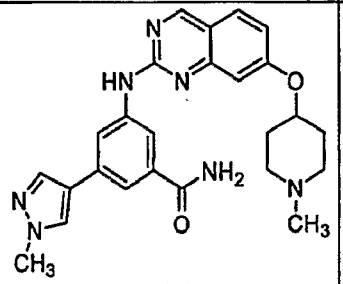
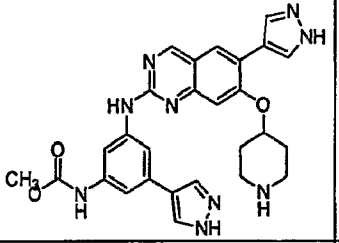
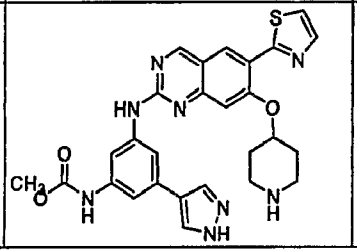
649		morpholino(4-(7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)methanone	517, 2.21	Example 27	++++	++++	++++	
650		6-bromo-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	484/486 2.02	Example 27	++++		++++	
651		N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-amine	472, 1.55	Example 27	++++			++++

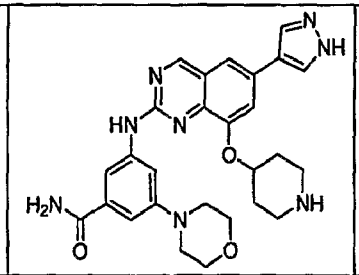
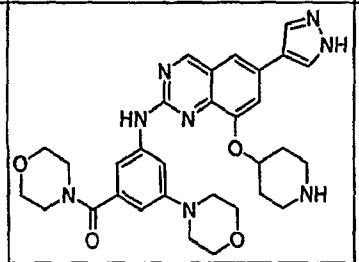
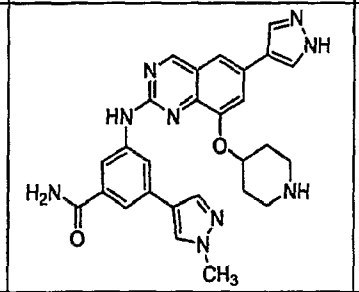
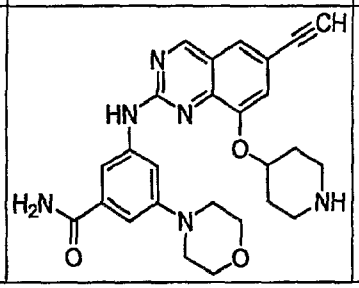
WO 2007/117607 PCT/US2007/008592

652		6-(isoxazol-4-yl)-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine	473, 1.68	Example 27	++++	++++		++++
653		7-(1-methylpiperidin-4-yloxy)-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	503, 1.97	Example 27	++++	++++		++++
654		7-(1-methylpiperidin-4-yloxy)-N-(4-morpholinophenyl)-6-(1H-pyrazol-4-yl)quinazolin-2-amine	486, 1.73	Example 27	++++			++++

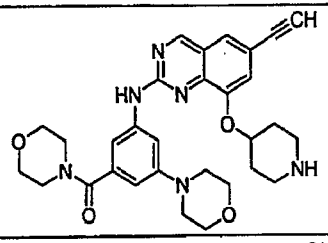
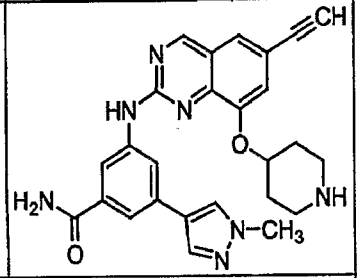
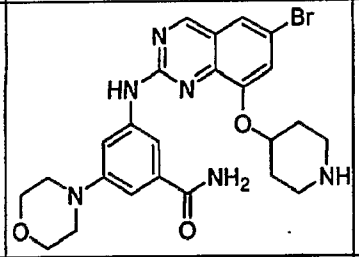
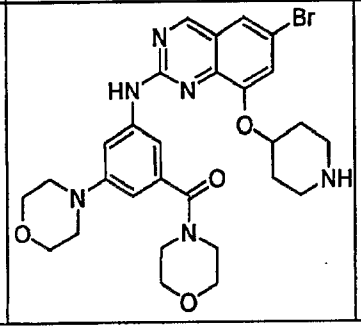
WO 2007/117607 PCT/US2007/008592

655		7-(1-methylpiperidin-4-yloxy)-N-(4-morpholinophenyl)quinazolin-2-amine	420, 1.72	Example 37	++++			++++
656		methyl 3-(morpholinomethyl)-5-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenylcarbamate	493.2	Example 2	++++			++++
657		N-(3-(6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(pyrimidin-5-yl)phenyl)acetamide	480.0, 2.05	Example 23 step 2, using 3-acetamido-5-iodoaniline; step 3d using pyrimidine-5-boronic acid; step 3a; step 4	++++			++++
658		N,N'-(5-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)-1,3-phenylene)diacetamide	435, 1.68	Example 37	++++			+++

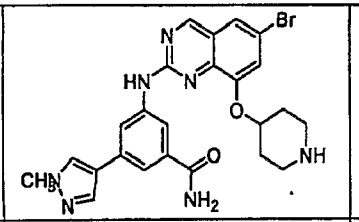
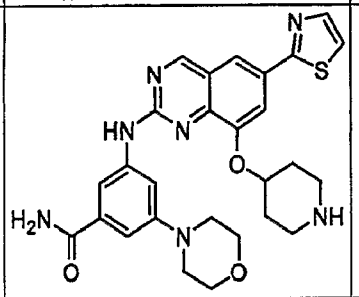
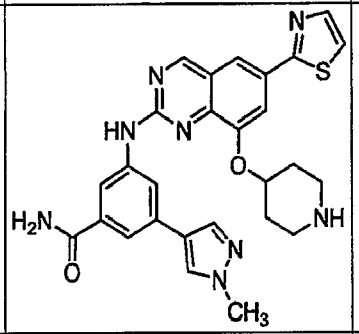
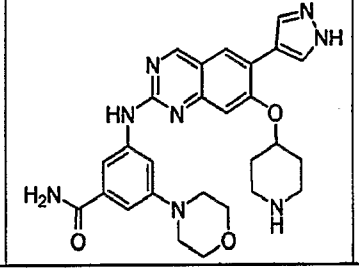
659		N-(3-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide	444, 1.73	Example 37	++++			+++
660		3-(1-methyl-1H-pyrazol-4-yl)-5-(7-(1-methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzamide	458.1, 1.78	Example 42 and Example 32	++++			++++
661		methyl 3-(7-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenylcarbamate	526, 1.79	Example 303, 306	++++			++++
662		methyl 3-(7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenylcarbamate	543, 2.03	Example 303, 306	++++			++++

663		3-morpholino-5-(8-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzamide	515.1, 1.79	Example 23 step 2, using 3-carboxamido-5-morpholinoaniline; step 3d, using N-Boc-4-pyrazole-boronic acid	++++			+++
664		morpholino(3-morpholino-5-(8-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)methanone	585.1, 1.90	Example 23 step 2, using 3-morpholinocarboxamide-5-morpholinoaniline; step 3d, using N-Boc-4-pyrazole-boronic acid	++++			+++
665		3-(1-methyl-1H-pyrazol-4-yl)-5-(8-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzamide	510.1, 1.83	Example 23 step 2, using 3-carboxamido-5-(1-methyl)pyrazol-4-ylaniline; step 3d, using N-Boc-4-pyrazole-boronic acid; step 4	++++			+++
666		3-(6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-morpholinobenzamide	473.0, 1.98	Example 23 step 2, using 3-carboxamido-5-morpholinoaniline; step 3a	++++			+++

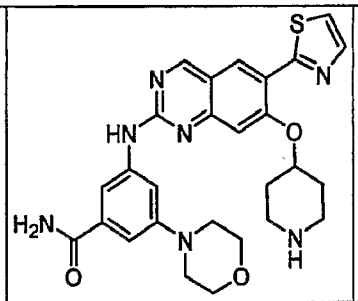
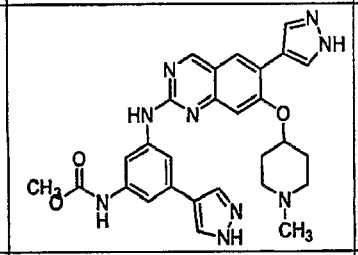
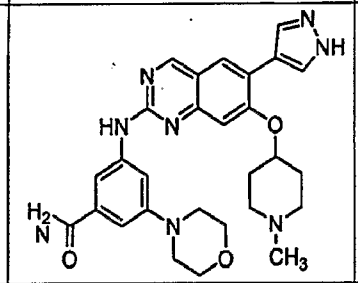
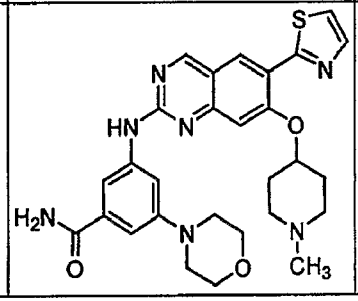
WO 2007/117607 PCT/US2007/008592

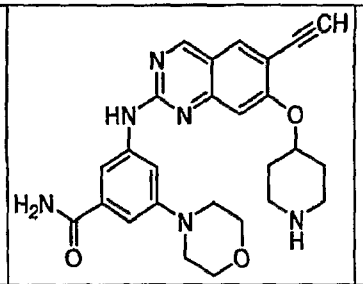
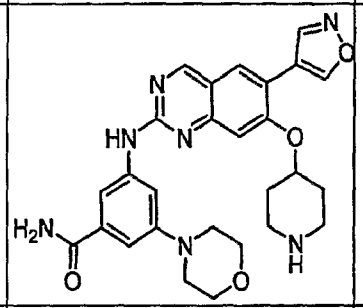
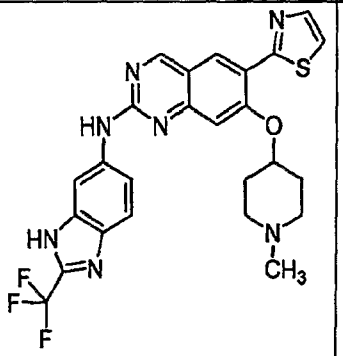
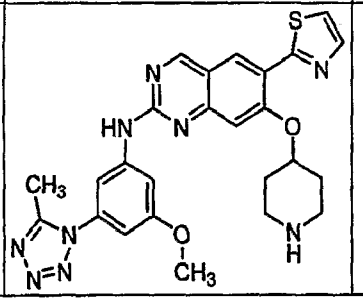
667		(3-(6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-morpholinophenyl)(morpholino)methanone	543.1, 2.11	Example 23 step 2, using 3-morpholinocarboxamide-5-morpholinoaniline; step 3a	++++			++++
668		3-(6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)benzamide	468.1, 2.01	Example 23 step 2, using 3-carboxamido-5-(1-methyl)pyrazol-4-ylaniline; step 3a; step 4	++++			++++
669		3-(6-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-morpholinobenzamide	528.9, 2.03	Example 23 step 2, using 3-carboxamido-5-morpholinoaniline	++++			+++
670		(3-(6-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-morpholinophenyl)(morpholino)methanone	599.0, 2.16	Example 23 step 2, using 3-morpholinocarboxamide-5-morpholinoaniline	++++			++++

WO 2007/117607 PCT/US2007/008592

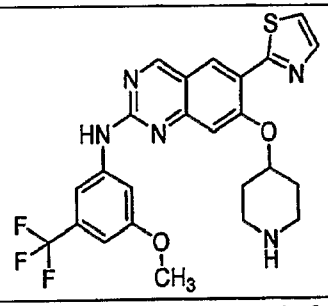
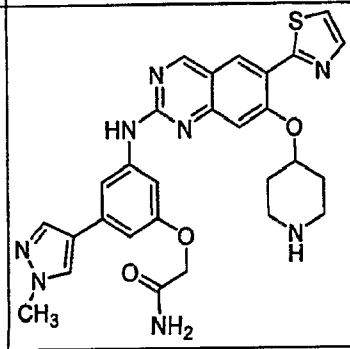
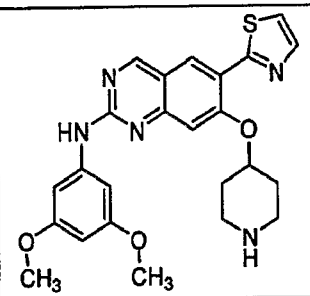
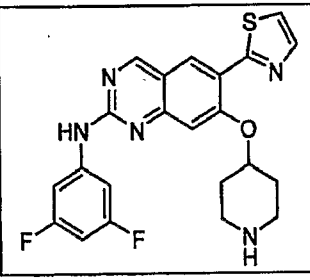
671		3-(6-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)benzamide	523.9, 2.07	Example 23 step 2, using 3-carboxamido-5-(1-methyl)pyrazol-4-ylaniline; step 4	++++			++++
672		3-morpholino-5-(8-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide	532.1, 2.09	Example 23 step 2, using 3-carboxamido-5-morpholinoaniline; step 3c	++++			+++
673		3-(1-methyl-1H-pyrazol-4-yl)-5-(8-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide	527.2, 2.13	Example 23 step 2, using 3-carboxamido-5-(1-methyl)pyrazol-4-ylaniline; step 3c	++++			+++
674		3-morpholino-5-(7-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzamide	515, 1.77	Example 27	++++			+++

WO 2007/117607 PCT/US2007/008592

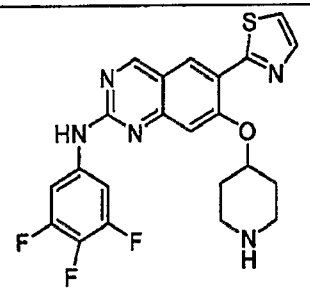
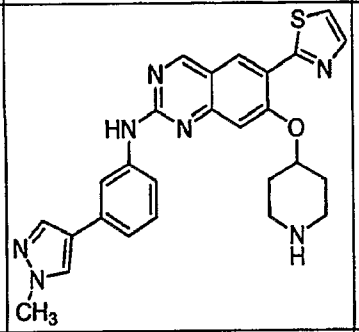
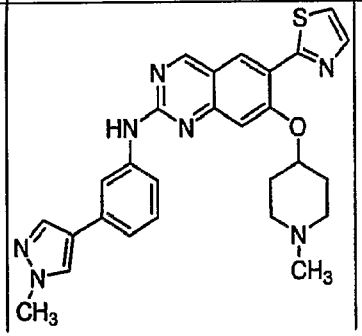
675		3-morpholino-5-(7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide	532, 1.94	Example 27	++++			+++
676		methyl 3-(7-(1-methylpiperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenylcarbamate	540, 1.83	Example 27	++++			++++
677		3-(7-(1-methylpiperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-morpholinobenzamide	529, 1.72	Example 27	++++			+++
678		3-(7-(1-methylpiperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-morpholinobenzamide	546, 1.90	Example 27	++++			++++

679		3-(6-ethynyl-7-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-morpholinobenzamide	473, 1.86	Example 27	++++			+++
680		3-(6-(isoxazol-4-yl)-7-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-morpholinobenzamide	516, 1.85	Example 27	++++			+++
681		7-(1-methylpiperidin-4-yloxy)-6-(thiazol-2-yl)-N-(2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)quinazolin-2-amine	526.1, 2.2	Example 27	++++			+++
682		N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	516, 2.21	Similar to Example 53	++++			++++

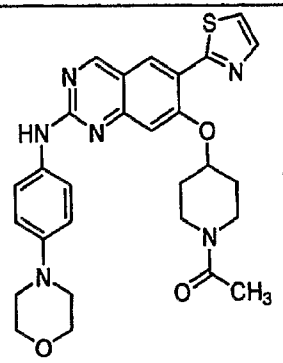
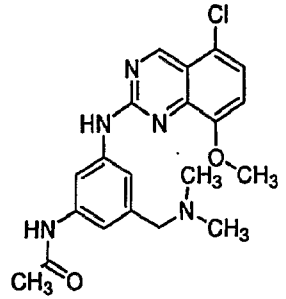
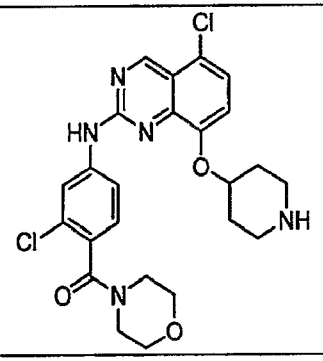
WO 2007/117607 PCT/US2007/008592

683		N-(3-methoxy-5-(trifluoromethyl)phenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	502, 2.58	Similar toExample 53				
684		2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)phenoxy)acetamide	557, 1.99	Similar to Example 53				
685		N-(3,5-dimethoxyphenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	464, 2.2	Similar to Example 53				
686		N-(3,5-difluorophenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	440, 2.42	Similar to Example 53				

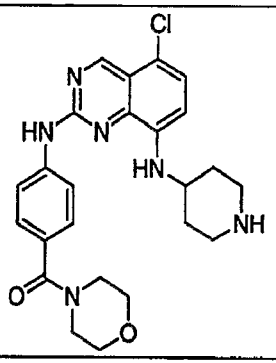
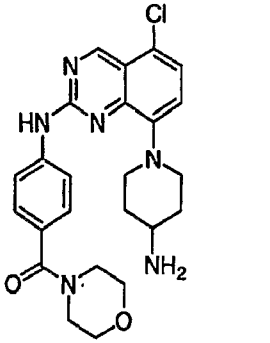
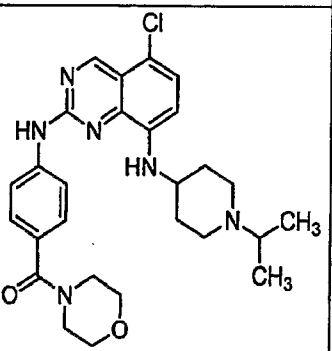
WO 2007/117607 PCT/US2007/008592

687		7-(piperidin-4-yloxy)-6-(thiazol-2-yl)-N-(3,4,5-trifluorophenyl)quinazolin-2-amine	458, 2.47	Similar to Example 53				
688		N-(3-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	484.2, 2.55	Example 27				
689		N-(3-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-(1-methylpiperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	498.2, 2.6	Example 27				

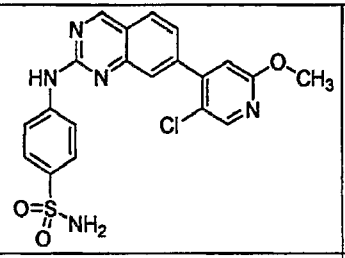
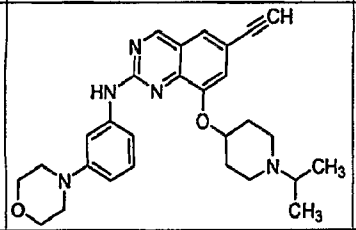
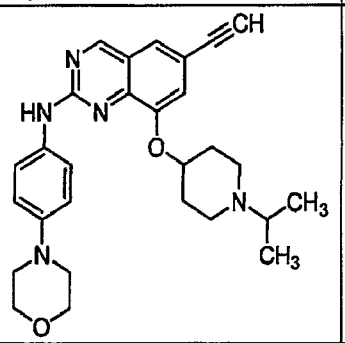
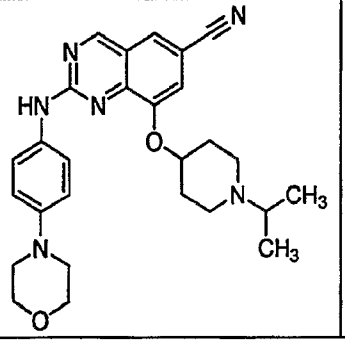
WO 2007/117607 PCT/US2007/008592

690		1-(4-(2-(4-morpholinophenylamino)-6-(thiazol-2-yl)quinazolin-7-yloxy)piperidin-1-yl)ethanone	531, 2.18	Example 27	++++			++++
691		N-(3-(5-chloro-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)acetamide	400.2, 2.12	Similar to Example 49	++++		+++	
692		(2-chloro-4-(5-chloro-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	502.2, 2.29	Similar to Example 48	++++		++++	

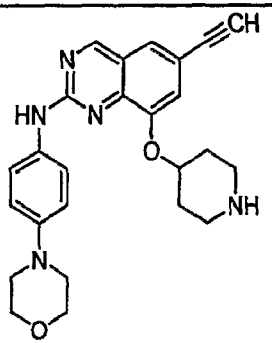
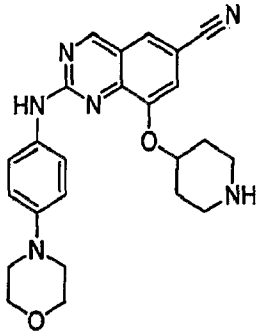
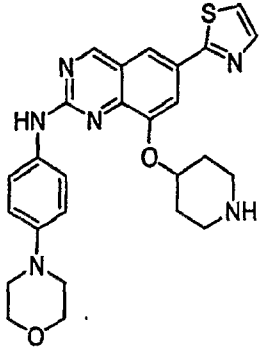
WO 2007/117607 PCT/US2007/008592

693		(4-(5-chloro-8-(piperidin-4-ylamino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	467.2, 2.27	Similar to example 50	++++		++++	
694		(4-(8-(4-aminopiperidin-1-yl)-5-chloroquinazolin-2-ylamino)phenyl)(morpholino)methanone	467.2, 2.10	Similar to example 50	++++		++++	
695		(4-(5-chloro-8-(1-isopropylpiperidin-4-ylamino)quinazolin-2-ylamino)phenyl)(morpholino)methanone	509.2, 2.38	Similar to example 50	++++		+++	

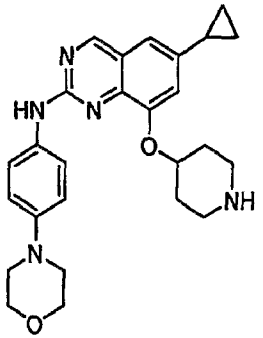
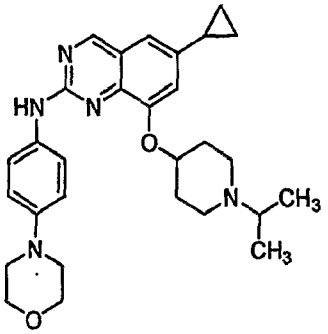
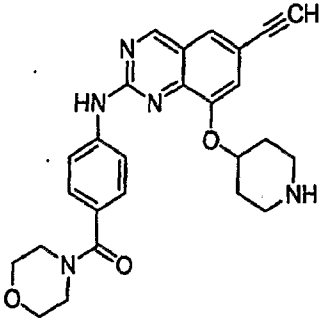
WO 2007/117607 PCT/US2007/008592

696		4-(7-(5-chloro-2-methoxypyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide	442.1	Similar to example 29	+	+++		
697		6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)-N-(3-morpholinophenyl)quinazolin-2-amine	472.2, 2.23	Similar to example 22	++++		++++	
698		6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)quinazolin-2-amine	472.2, 2.06	Similar to example 22, using 4-morpholinoaniline in place of 3-morpholinoaniline	++++		++++	
699		8-(1-isopropylpiperidin-4-yloxy)-2-(4-morpholinophenylamino)quinazoline-6-carbonitrile	473.2, 2.02	Similar to example 22 step 1 using 4-morpholinoaniline in place of 3-morpholinoaniline	++++		++++	

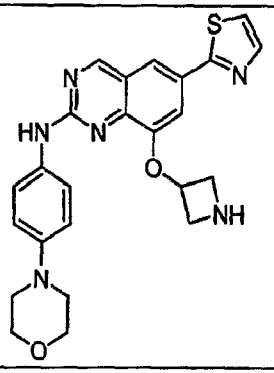
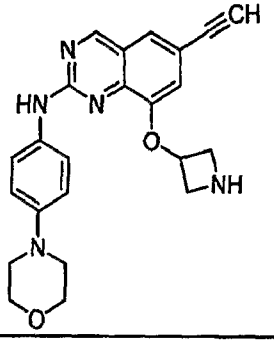
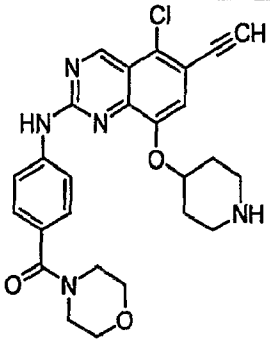
WO 2007/117607 PCT/US2007/008592

700		6-ethynyl-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	430.1, 2.00	Example 23, steps 1, 2, 3a, and 4	++++		++++	
701		2-(4-morpholinophenylamino)-8-(piperidin-4-yloxy)quinazoline-6-carbonitrile	431.1, 1.92	Example 23, steps 1, 2, 3b, and 4	++++		++++	
702		N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine	489.1, 2.02	Example 23, steps 1, 2, 3c, and 4	++++		++++	

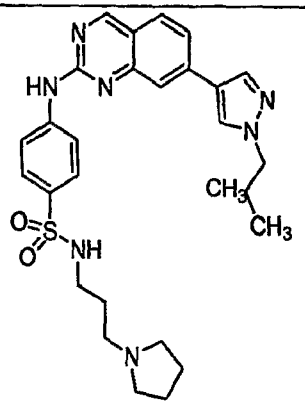
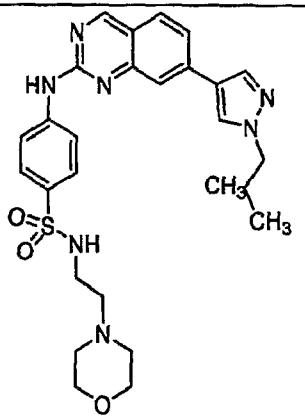
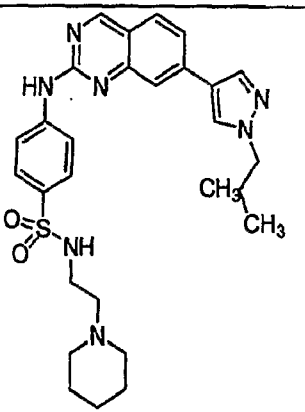
WO 2007/117607 PCT/US2007/008592

703		6-cyclopropyl-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine	446.2, 2.05	Example 23, steps 1, 2, 3d, and 4	++++		++++	
704		6-cyclopropyl-8-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)quinazolin-2-amine	488.3, 2.14	Example 23, steps 1, 2, 3d, and 4	++++		++++	
705		(4-(6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	458.2, 2.03	Example 23, steps 1, 2, 3a, and 4, using (4-aminophenyl)(morpholino)methanone in place of 4-morpholinoaniline	++++		++++	

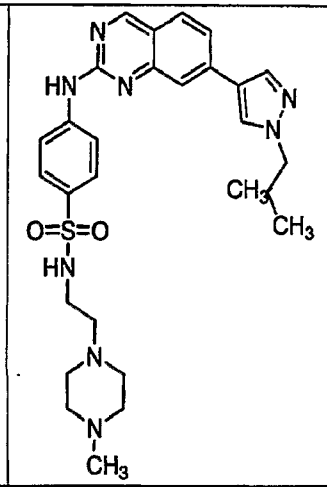
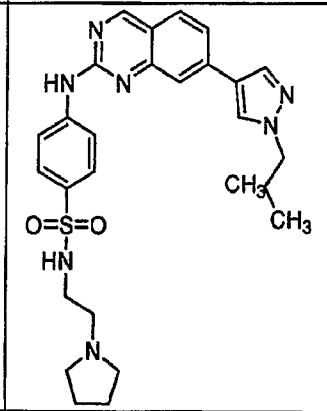
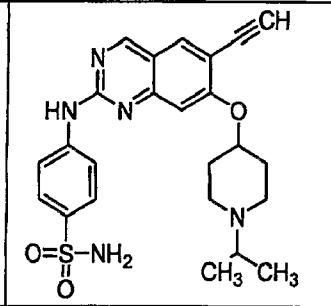
WO 2007/117607 PCT/US2007/008592

706		8-(azetidin-3-yloxy)-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	461.1, 1.93	Example 23 steps 1, 2, 3c, and 4, using N-tert-butyl 3-hydroxy-1-azetidine carboxylate in place of N-tert-butyl 4-hydroxy-1-piperidine carboxylate	++++		++++	
707		8-(azetidin-3-yloxy)-6-ethynyl-N-(4-morpholinophenyl)quinazolin-2-amine	402.2, 1.89	Example 23, steps 1, 2, 3a, and 4, using N-tert-butyl 3-hydroxy-1-azetidine carboxylate in place of N-tert-butyl 4-hydroxy-1-piperidine carboxylate	++++		++++	
708		(4-(5-chloro-6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	492.2, 2.26	Example 9 using 6-bromo-2,5-dichloro-8-methoxyquinazoline in place of 1b, then analogous to 23a	++++		++++	

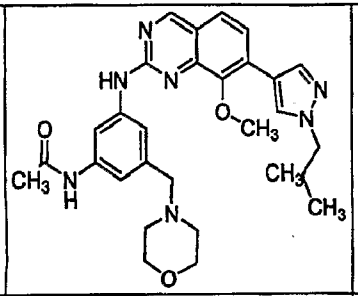
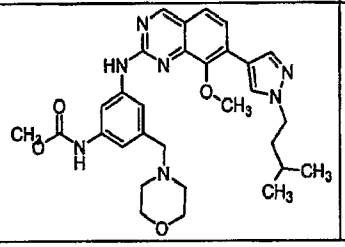
WO 2007/117607 PCT/US2007/008592

709		4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(3-(pyrrolidin-1-yl)propyl)benzenesulfonamide	534, 3.05	Example 25	++++		++++	
710		44-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(2-morpholinoethyl)benzenesulfonamide	536, 2.88	Example 25	++++		++++	
711		4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(2-(piperidin-1-yl)ethyl)benzenesulfonamide	534, 3.01	Example 25	++++		++++	

WO 2007/117607 PCT/US2007/008592

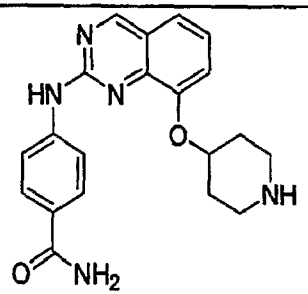
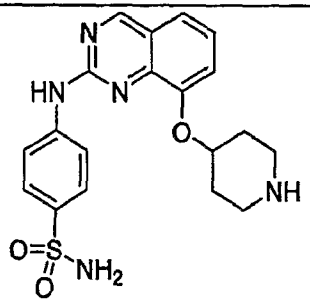
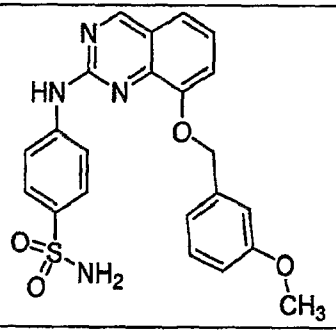
712		4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(2-(4-methylpiperazin-1-yl)ethyl)benzenesulfonamide	549, 2.62	Example 25	++++		++++	
713		4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(2-(pyrrolidin-1-yl)ethyl)benzenesulfonamide	520, 2.97	Example 25	++++		++++	
714		4-(6-ethynyl-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide	466, 3.20	Example 27	++++		++++	

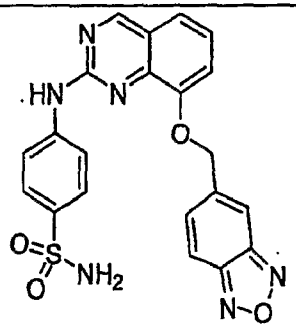
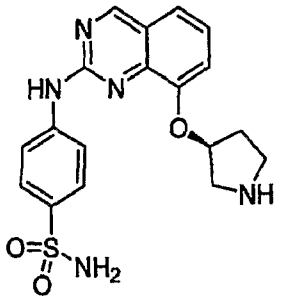
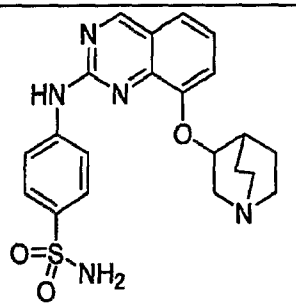
WO 2007/117607 PCT/US2007/008592

715		N-(3-(7-(1-isobutyl-1H-pyrazol-4-yl)-8-methoxyquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide	530.2. 2.12	Example 5, then Example 9 step 3, Example 35, step 2 and 4	++++			++++
716		methyl 3-(7-(1-isopentyl-1H-pyrazol-4-yl)-8-methoxyquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl carbamate	560.2, 2.51	Example 5, then Example 9 step 3, Example 35, step 2 and 4	++++			++++

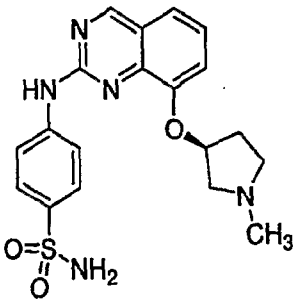
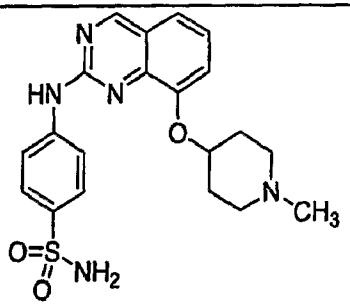
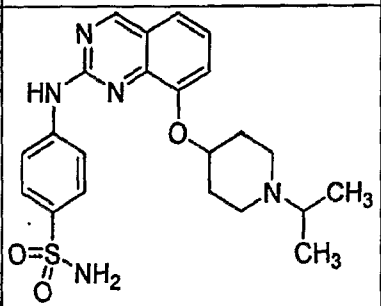
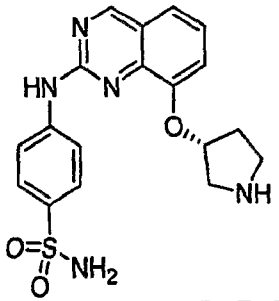
WO 2007/117607 PCT/US2007/008592

Table 4

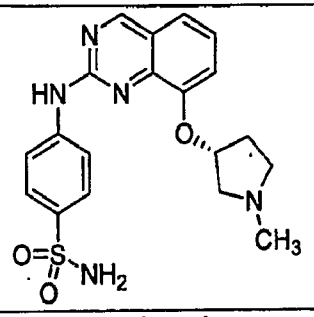
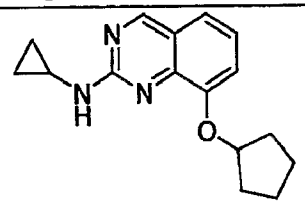
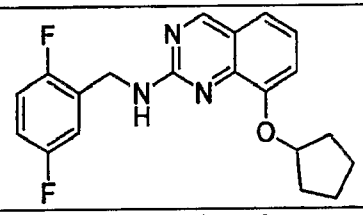
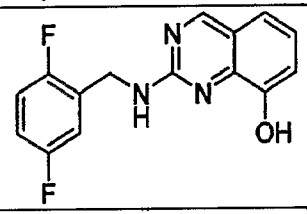
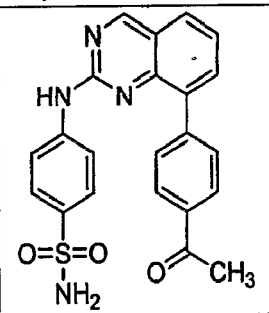
Cmpd	Structure	Name	LC/MS (M+1(m/z), Rt(min))	Synthetic method	PDK1 IC_{50}	$CPEC_{50}$ A2780	$CPEC_{50}$ PC3	$CPEC_{50}$ PC3MM
717.		4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzamide		Example 20, steps 2 and 3, using 4-aminoacetanilide in place of (4-aminophenyl)(morpholino)methanone	++++	++++		++++
718.		4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide		Example 20, steps 2 and 3, using sulfanilamide in place of (4-aminophenyl)(morpholino)methanone	++++	++++	++++	++++
719.		4-(8-(3-methoxybenzyloxy)quinazolin-2-ylamino)benzenesulfonamide			+	++++		+

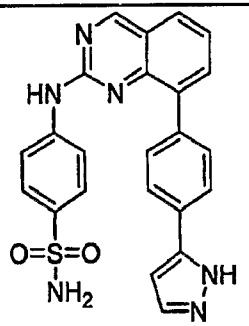
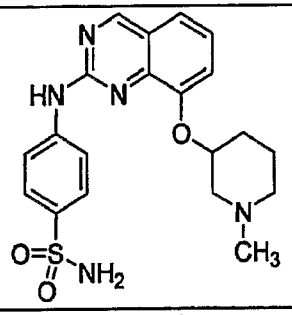
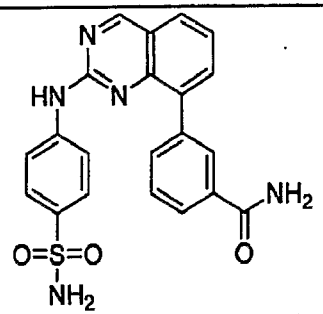
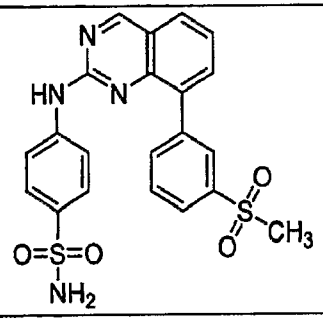
720.		4-(8-(benzo[c][1,2,5]oxadiazol-5-ylmethoxy)quinazolin-2-ylamino)benzenesulfonamide			+	+++		+
721		(S)-4-(8-(pyrrolidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
722.		4-(8-(quinuclidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

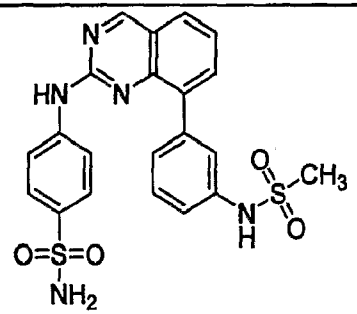
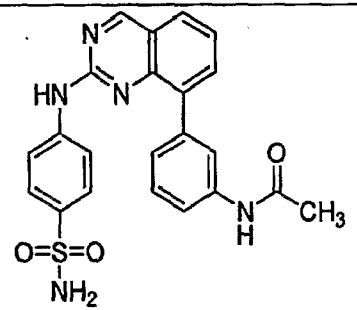
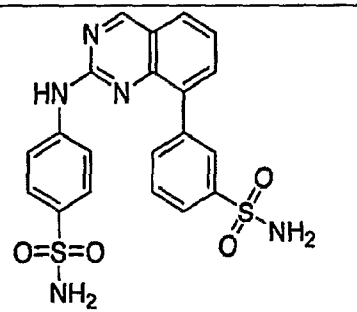
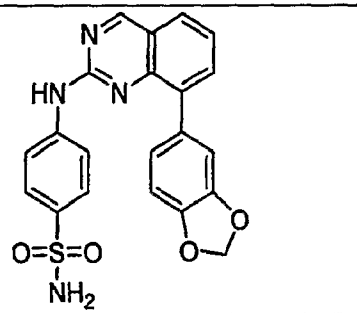
WO 2007/117607 PCT/US2007/008592

723.		(S)-4-(8-(1-methylpyrrolidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
724.		4-(8-(1-methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
725.		4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
726.		(R)-4-(8-(pyrrolidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

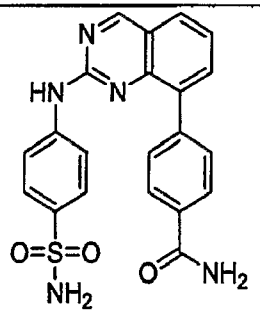
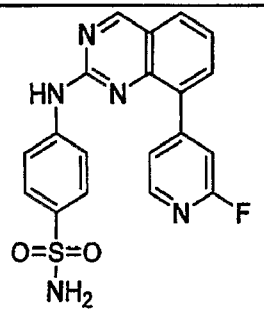
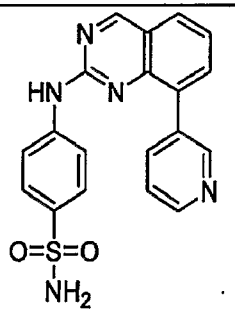
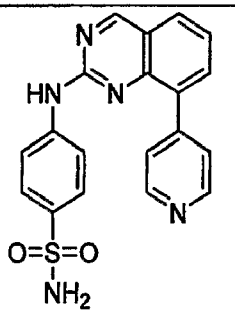
WO 2007/117607 PCT/US2007/008592

727.		(R)-4-(8-(1-methylpyrrolidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
728.		8-(cyclopentyloxy)-N-cyclopropylquinazolin-2-amine			+	+++		+
729.		8-(cyclopentyloxy)-N-(2,5-difluorobenzyl)quinazolin-2-amine			+	+++		+
730.		2-(2,5-difluorobenzylamino)quinazolin-8-ol			+	++++		+
731.		4-(8-(4-acetylphenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++

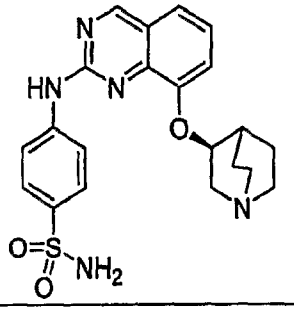
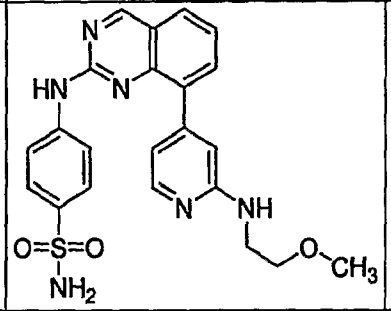
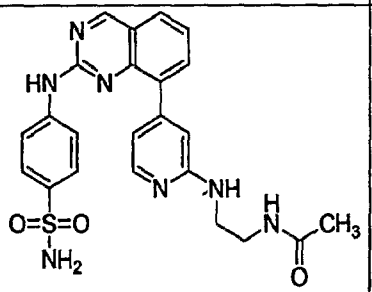
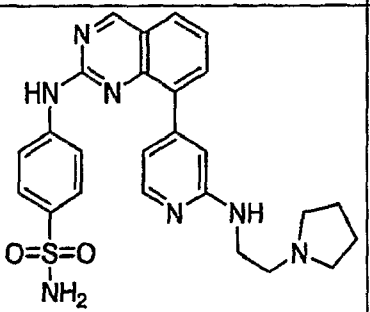
732.		4-(8-(4-(1H-pyrazol-5-yl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
733.		4-(8-(1-methylpiperidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
734.		3-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)benzamide			++++	++++		++++
735.		4-(8-(3-(methylsulfonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

736.		4-(8-(3-(methylsulfonamido)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
737.		N-(3-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)phenyl)acetamide			++++	++++		++++
738.		3-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)benzenesulfonamide			++++	++++		++++
739.		4-(8-(benzo[d][1,3]dioxol-5-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

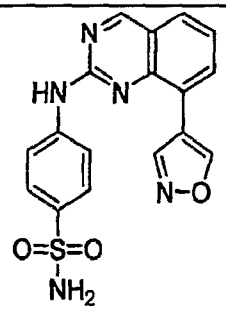
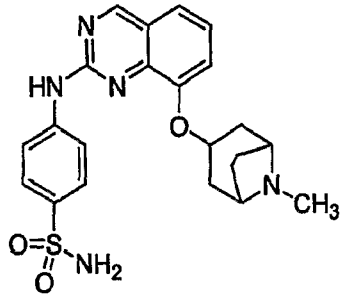
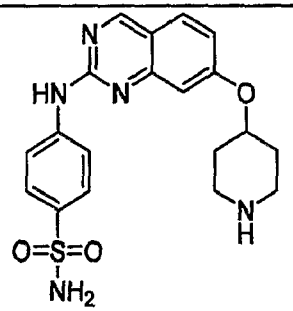
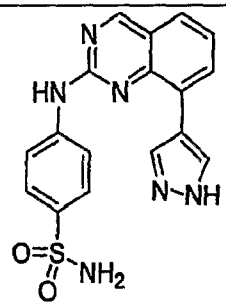
WO 2007/117607 PCT/US2007/008592

740.		4-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)benzamide			++++	+++		++++
741.		4-(8-(2-fluoropyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
742.		4-(8-(pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
743.		4-(8-(pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++

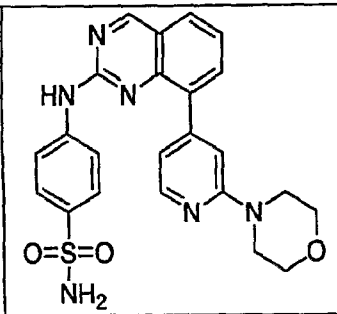
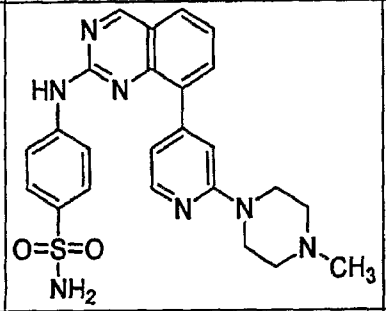
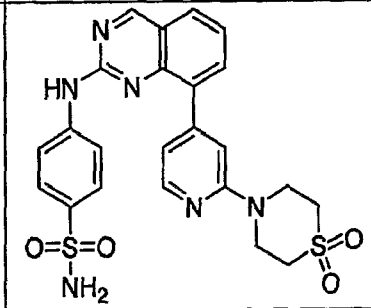
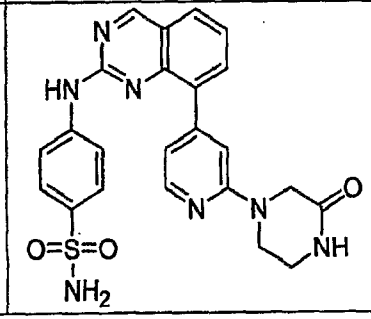
WO 2007/117607 PCT/US2007/008592

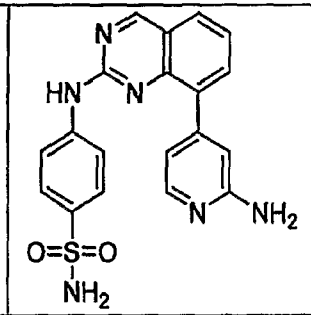
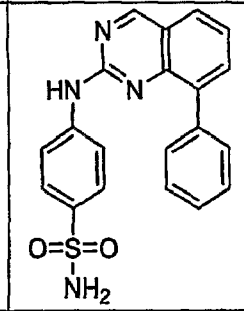
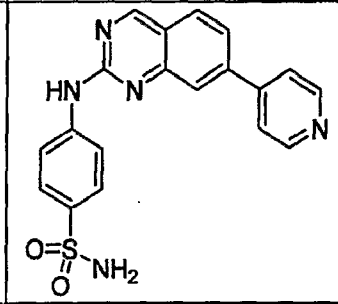
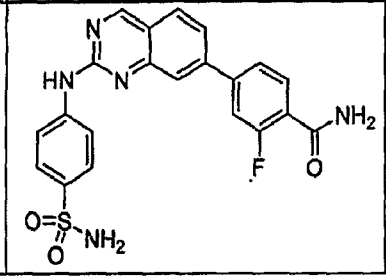
744.		(S)-4-(8-(quinuclidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
745.		4-(8-(2-(2-methoxyethylamino)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
746.		N-(2-(4-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)pyridin-2-ylamino)ethyl)acetamide			++++	+++		++++
747.		4-(8-(2-(2-(pyrrolidin-1-yl)ethylamino)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

WO 2007/117607 PCT/US2007/008592

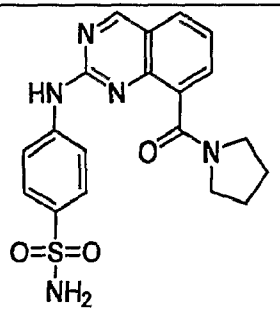
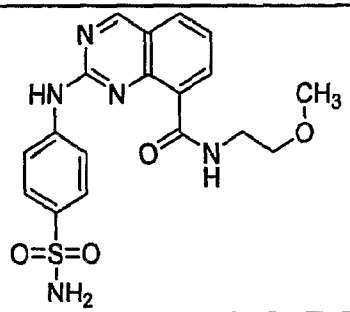
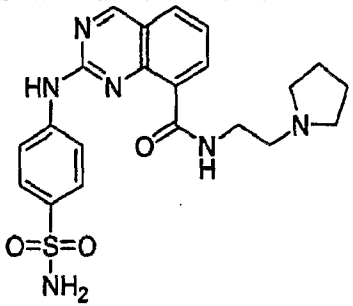
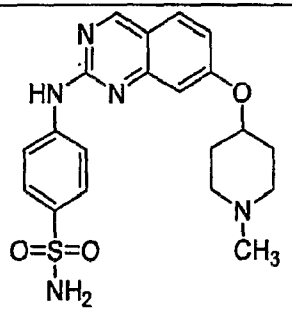
748.		4-(8-(isoxazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
749.		4-(8-(8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
750.		4-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
751.		4-(8-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

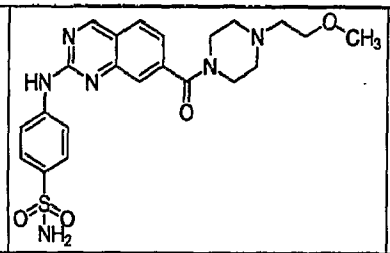
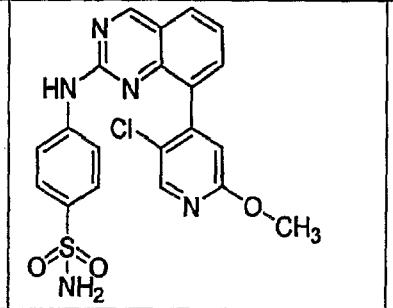
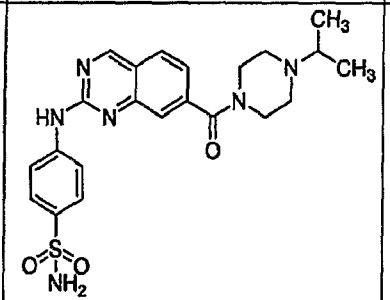
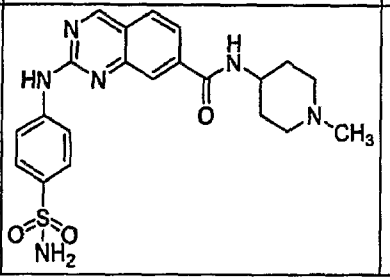
WO 2007/117607 PCT/US2007/008592

752.		4-(8-(2-morpholinopyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
753.		4-(8-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
754.					++++	++++		++++
755.		4-(8-(2-(3-oxopiperazin-1-yl)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

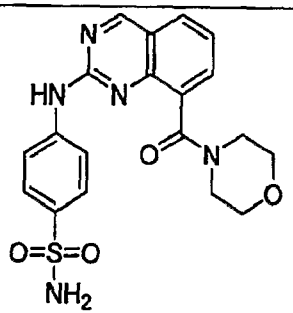
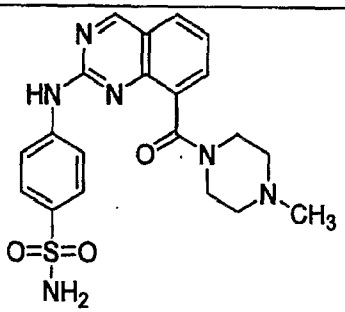
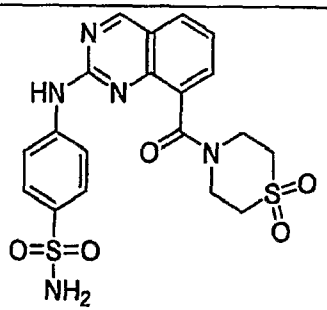
756.		4-(8-(2-aminopyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
757.		4-(8-phenylquinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
758.		4-(7-(pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide						
759.		2-fluoro-4-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzamide			++++	+++		++++

WO 2007/117607 PCT/US2007/008592

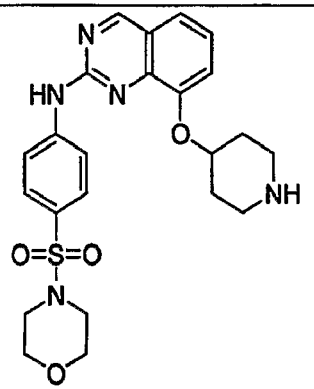
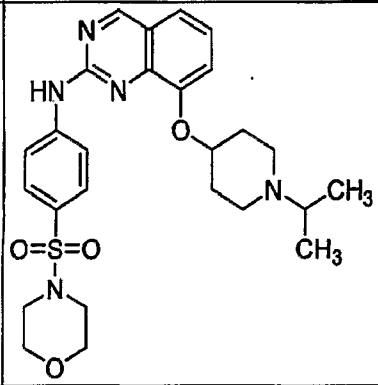
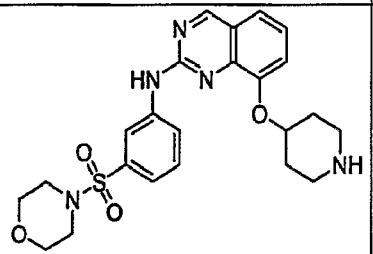
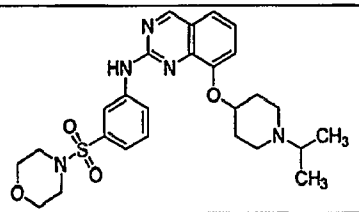
760.		4-(8-(pyrrolidine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
761.		N-(2-methoxyethyl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			++++	++++		+++
762.		N-(2-(pyrrolidin-1-yl)ethyl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			++++	++++		+++
763.		4-(7-(1-methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++

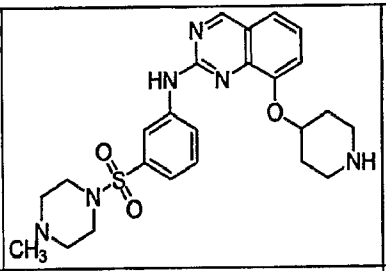
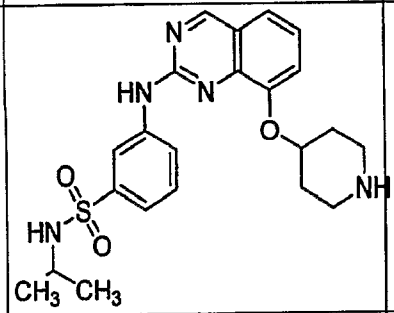
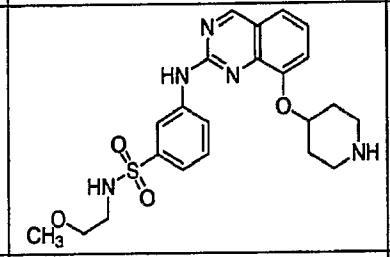
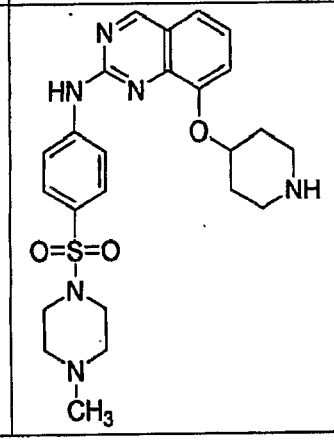
764.		4-(7-(4-(2-methoxyethyl)piperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++	+++		++
765.		4-(8-(5-chloro-2-methoxypyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
766.		4-(7-(4-isopropylpiperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++
767.		N-(1-methylpiperidin-4-yl)-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide			++++	+++		++++

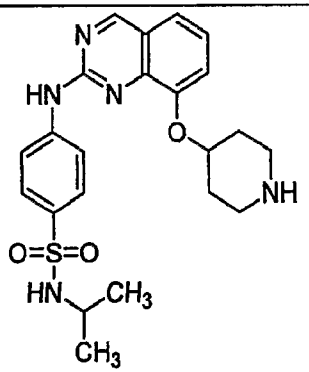
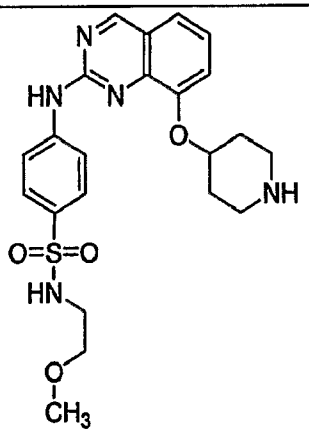
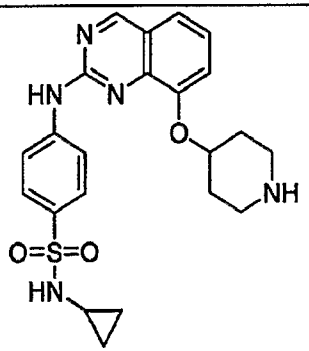
WO 2007/117607 PCT/US2007/008592

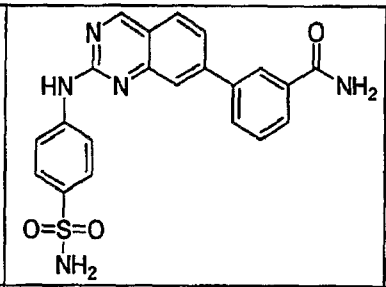
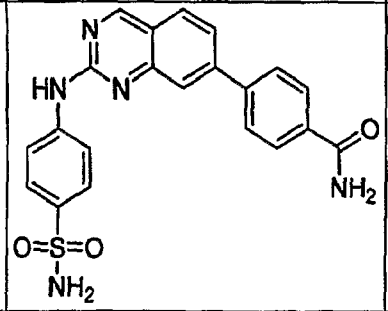
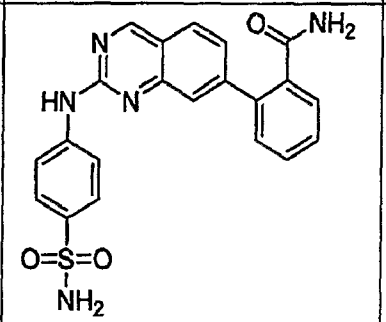
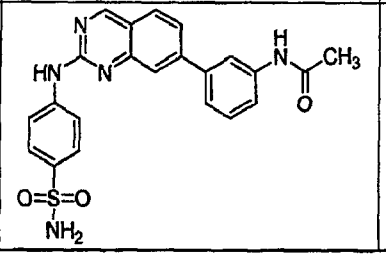
768.		4-(8-(*morpholine*-4-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			+++	+++		+++
769.		4-(8-(4-methylpiperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
770.					++	+++		++

WO 2007/117607 PCT/US2007/008592

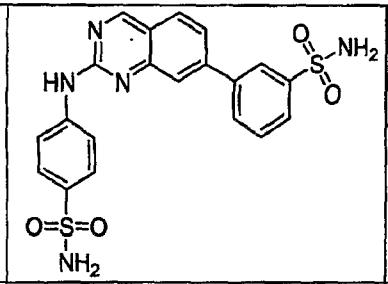
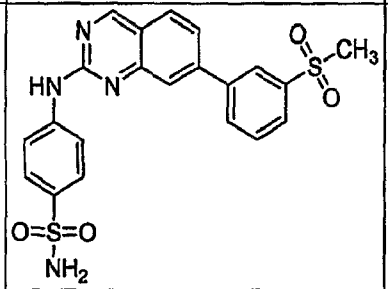
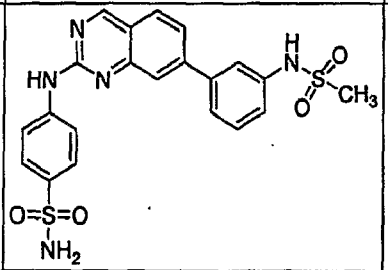
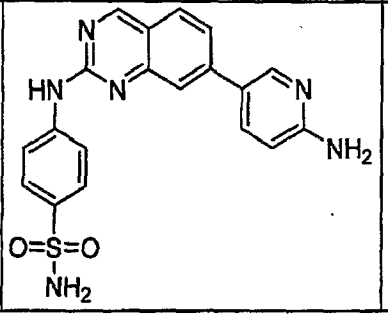
771.		N-(4-(morpholinosulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine			++++	++++	++++	++++
772.		8-(1-isopropylpiperidin-4-yloxy)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine			++++	++++	++++	++++
773.		N-(3-(morpholinosulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine			++++	++++		++++
774.		8-(1-isopropylpiperidin-4-yloxy)-N-(3-(morpholinosulfonyl)phenyl)quinazolin-2-amine			++++	++++		++++

775.		N-(3-(4-methylpiperazin-1-ylsulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine			++++	+++		++++
776.		N-isopropyl-3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
777.		N-(2-methoxyethyl)-3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
778.		N-(4-(4-methylpiperazin-1-ylsulfonyl)phenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine			++++	++++		++++

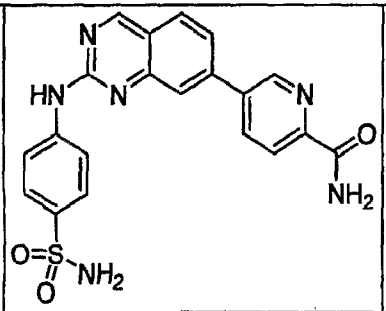
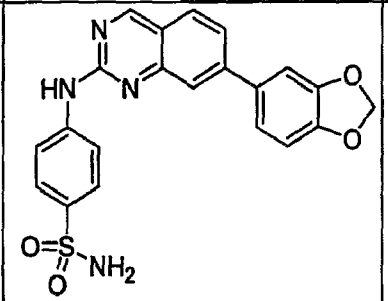
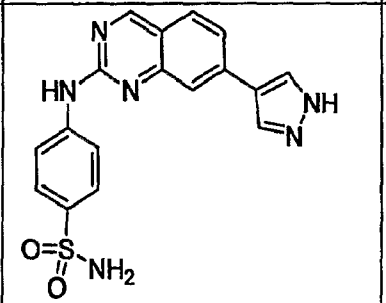
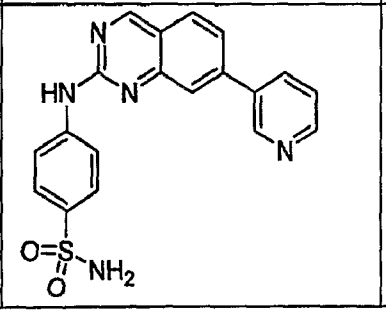
779.		N-isopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
780.		N-(2-methoxyethyl)-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
781.		N-cyclopropyl-4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++

782.		3-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzamide			++++	+++		++++
783.		4-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzamide			++++	+++		++++
784.		2-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzamide			++++			++++
785.		N-(3-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)phenyl)acetamide			+++			+++

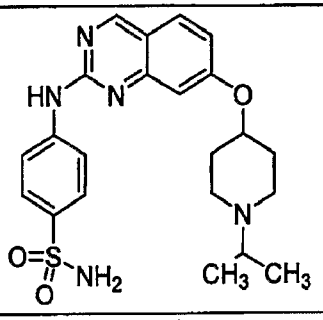
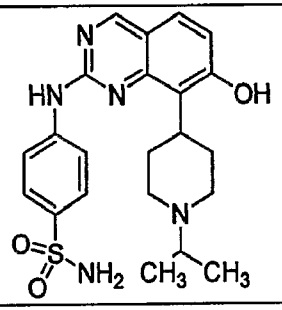
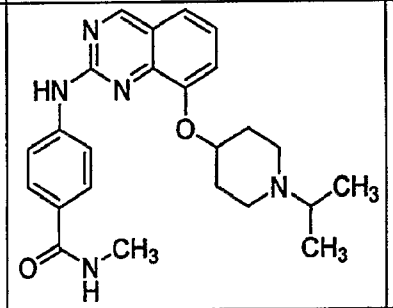
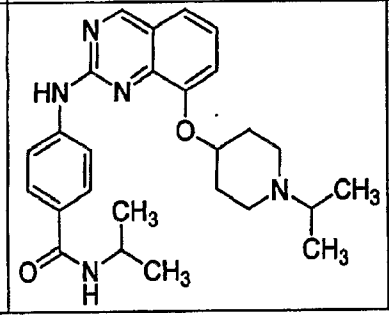
WO 2007/117607 PCT/US2007/008592

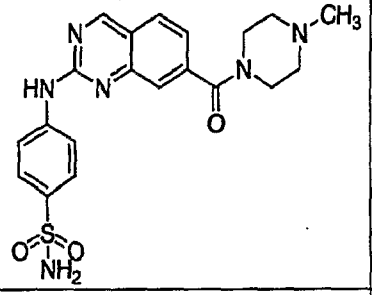
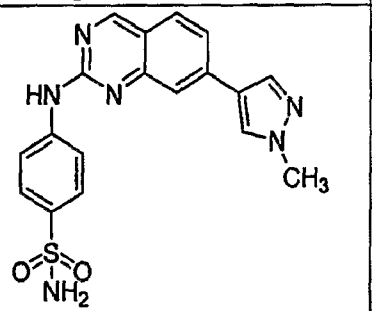
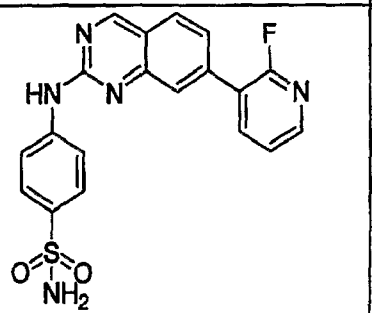
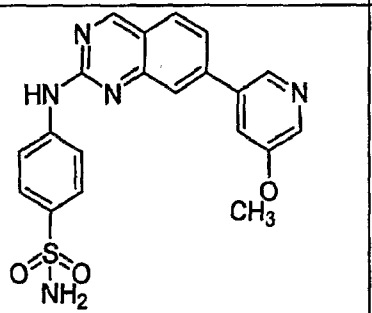
786.		3-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzenesulfonamide			++++	+++		++++
787.		4-(7-(3-(methylsulfonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++			++++
788.		4-(7-(3-(methylsulfonamido)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++			++
789.		4-(7-(6-aminopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

WO 2007/117607 PCT/US2007/008592

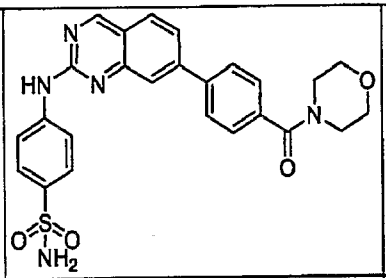
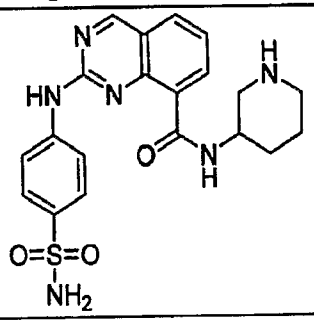
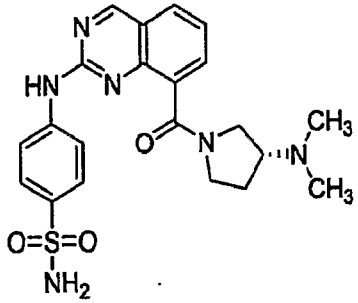
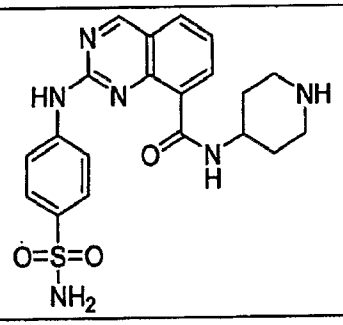
790.		5-(2-(4-sulfamoylphenylamino)quinazolin-7-yl)picolinamide			++++	+++		++++
791.		4-(7-(benzo[d][1,3]dioxol-5-yl)quinazolin-2-ylamino)benzenesulfonamide			+	+++		+
792.		4-(7-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
793.		4-(7-(pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

WO 2007/117607 PCT/US2007/008592

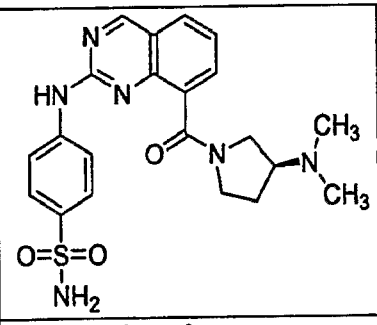
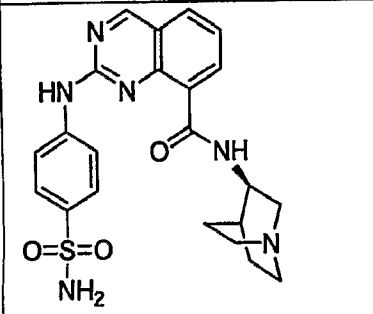
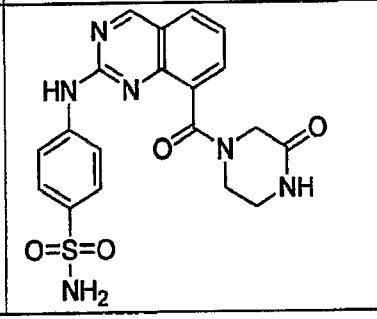
794.		4-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
795.		4-(7-hydroxy-8-(1-isopropylpiperidin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
796.		4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)-N-methylbenzamide			++++	++++		++++
797.		N-isopropyl-4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzamide			++++	++++	++++	++++

798.		4-(7-(4-methylpiperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++	+++		++
799.		4-(7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
800.		4-(7-(2-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
801.		4-(7-(5-methoxypyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

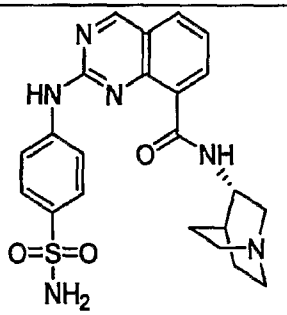
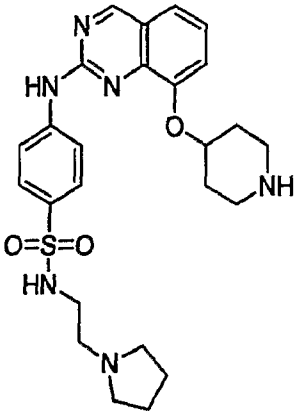
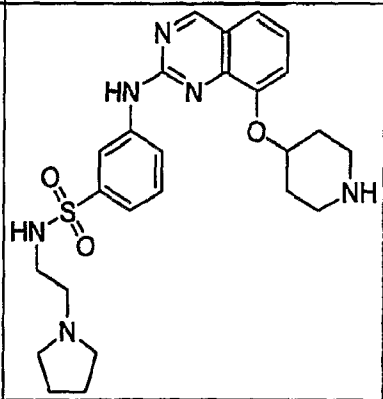
WO 2007/117607 PCT/US2007/008592

802.		4-(7-(4-(morpholine-4-carbonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
803.		N-(piperidin-3-yl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			++++	+++		++++
804.		(R)-4-(8-(3-(dimethylamino)pyrrolidine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
805.		N-(piperidin-4-yl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			++++	+++		++++

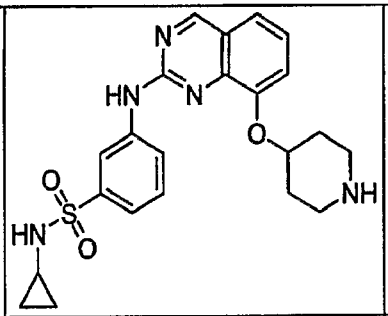
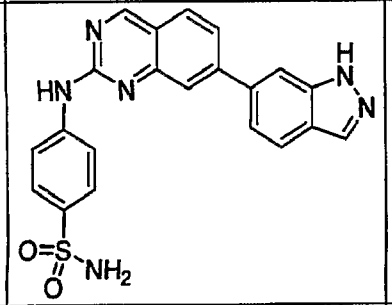
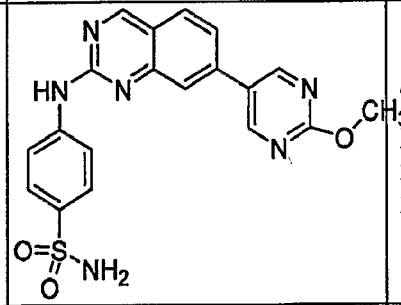
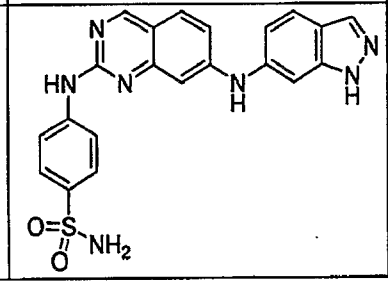
WO 2007/117607 PCT/US2007/008592

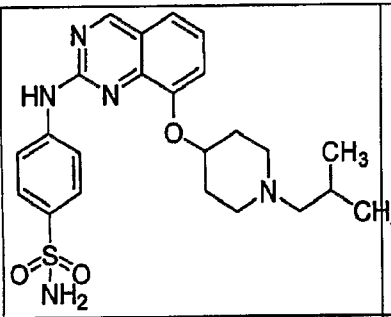
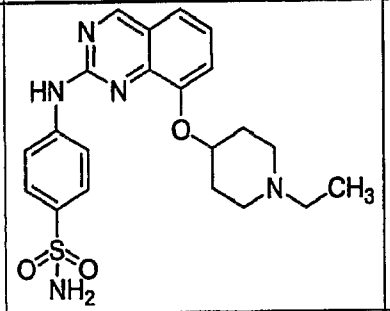
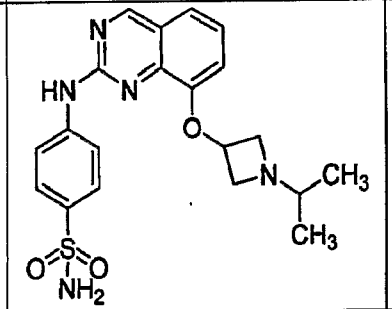
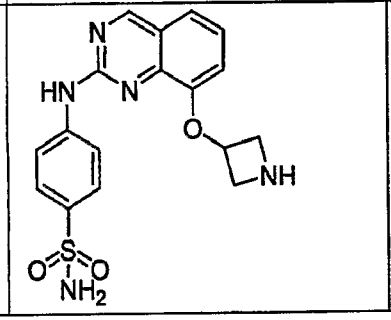
806.		(S)-4-(8-(3-(dimethylamino)pyrrolidine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
807.		(R)-N-(quinuclidin-3-yl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			+++	+++		+++
808.		4-(8-(3-oxopiperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++

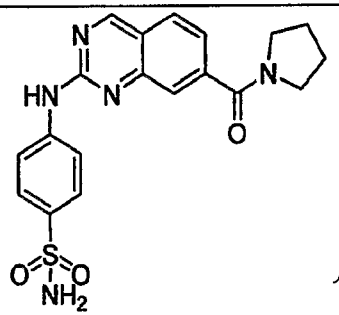
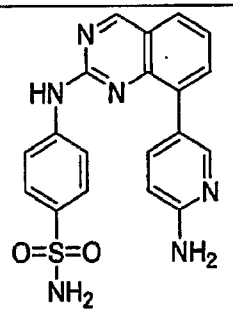
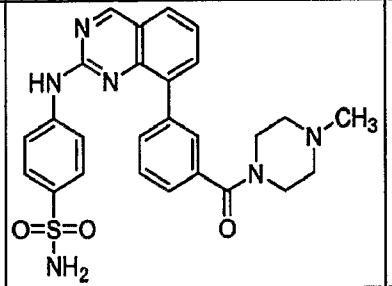
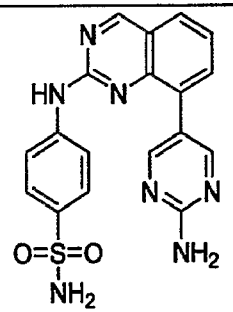
WO 2007/117607 PCT/US2007/008592

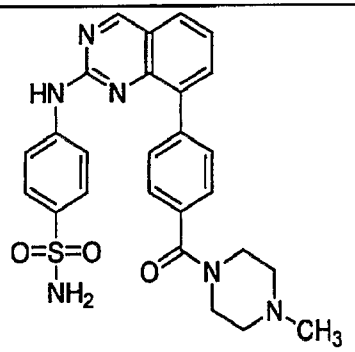
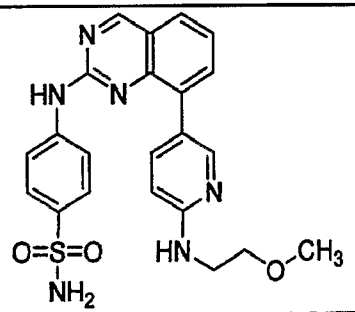
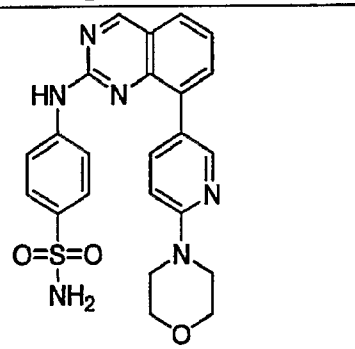
809.		(S)-N-(quinuclidin-3-yl)-2-(4-sulfamoylphenylamino)quinazoline-8-carboxamide			++++	+++		++++
810.		4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(2-(pyrrolidin-1-yl)ethyl)benzenesulfonamide			++++	++++	++++	++++
811.		3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)-N-(2-(pyrrolidin-1-yl)ethyl)benzenesulfonamide			++++	+++		++++

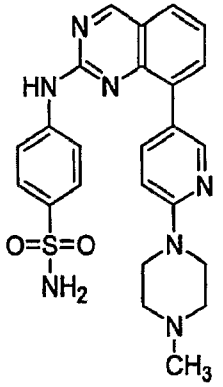
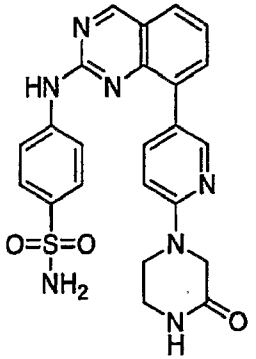
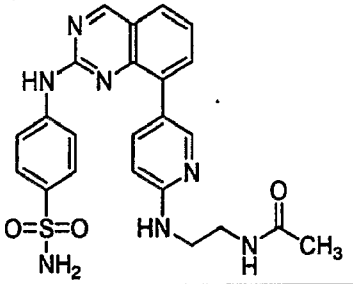
WO 2007/117607 PCT/US2007/008592

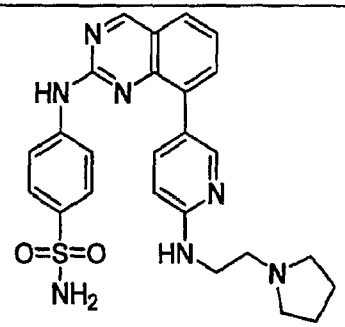
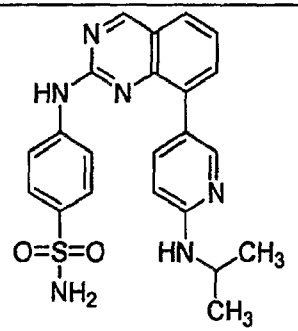
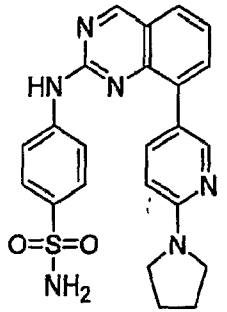
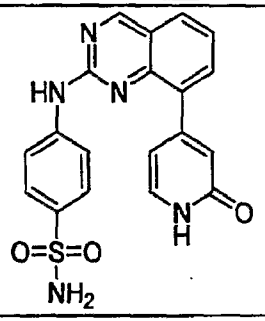
812.		N-cyclopropyl-3-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
813.		4-(7-(1H-indazol-6-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
814.		4-(7-(2-methoxypyrimidin-5-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
815.		4-(7-(1H-indazol-6-ylamino)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

816.		4-(8-(1-isobutylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
817.		4-(8-(1-ethylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
818.		4-(8-(1-isopropylazetidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
819.		4-(8-(azetidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++

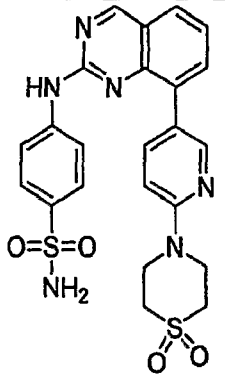
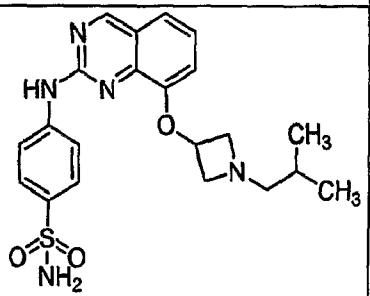
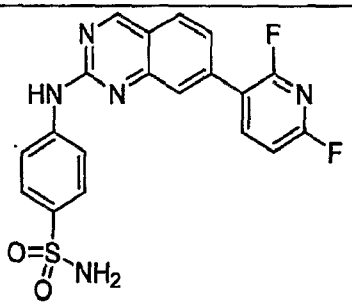
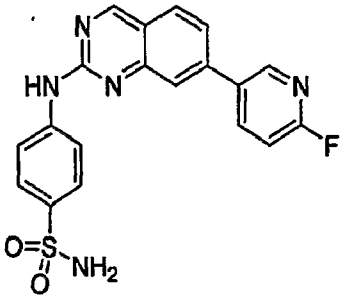
820.		4-(7-(pyrrolidine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
821.		4-(8-(6-aminopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
822.		4-(8-(3-(4-methylpiperazine-1-carbonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
823.		4-(8-(2-aminopyrimidin-5-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

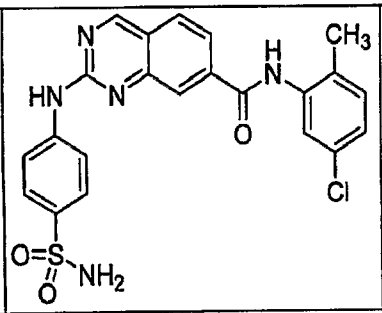
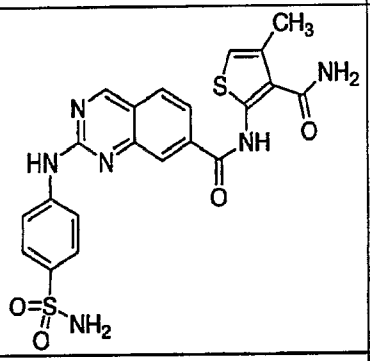
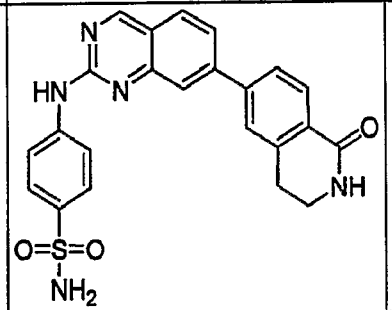
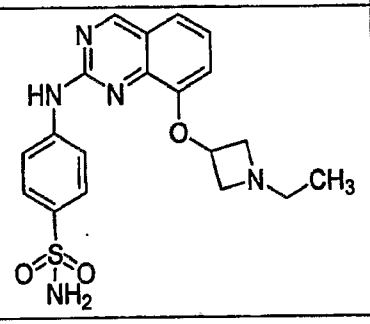
824.		4-(8-(4-(4-methylpiperazine-1-carbonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
825.		4-(8-(6-(2-methoxyethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
826.		4-(8-(6-morpholinopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

827.		4-(8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
828.		4-(8-(6-(3-oxopiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
829.		N-(2-(5-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)pyridin-2-ylamino)ethyl)acetamide			++++	++++		++++

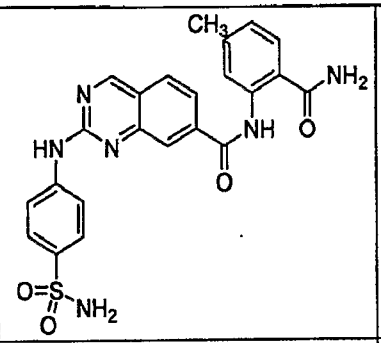
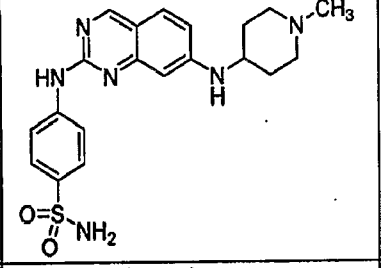
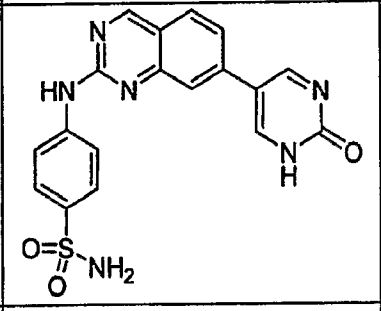
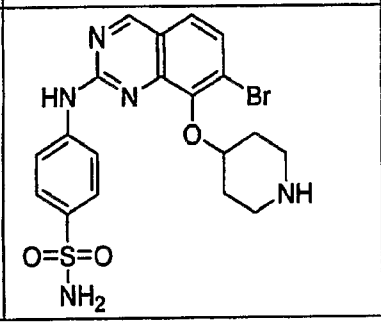
830.		4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
831.		4-(8-(6-(isopropylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
832.		4-(8-(6-(pyrrolidin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
833.		4-(8-(2-oxo-1,2-dihydropyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++

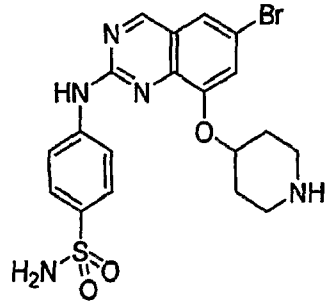
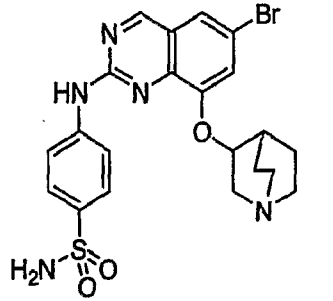
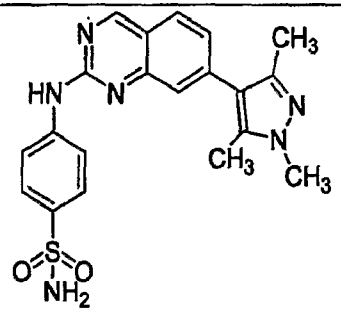
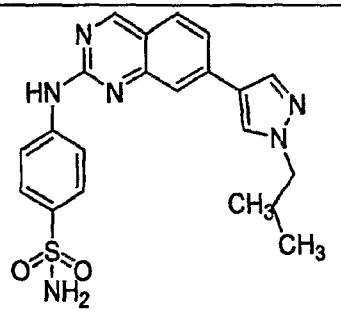
WO 2007/117607 PCT/US2007/008592

834.					++++	++++		++++
835.		4-(8-(1-isobutylazetidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
836.		4-(7-(2,6-difluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
837.		4-(7-(6-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

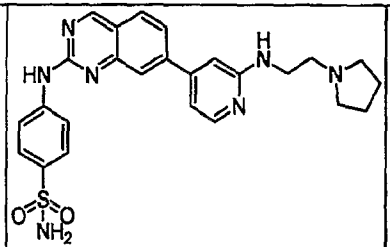
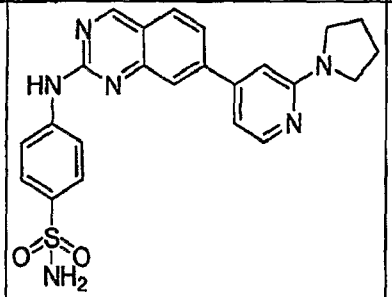
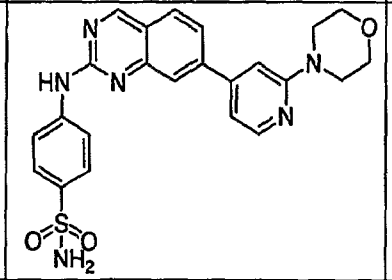
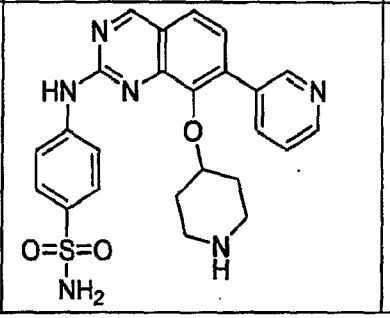
838.		N-(5-chloro-2-methylphenyl)-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide			++++	++++		++++
839.		N-(3-carbamoyl-4-methylthiophen-2-yl)-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide			++++	++++		++++
840.		4-(7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
841.		4-(8-(1-ethylazetidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

WO 2007/117607 PCT/US2007/008592

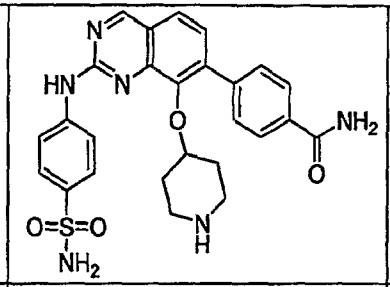
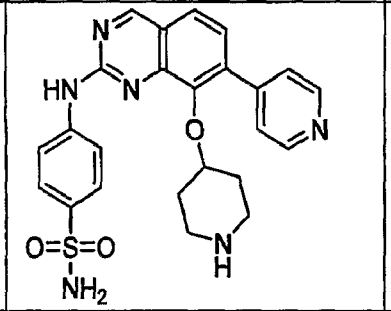
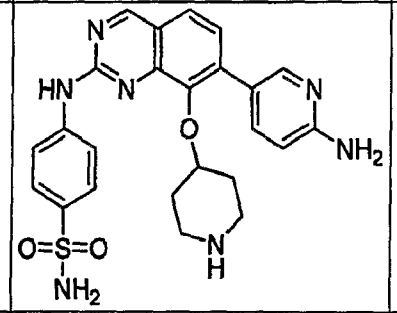
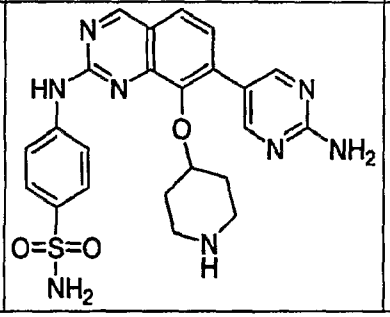
842.		N-(2-carbamoyl-5-methylphenyl)-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide			++++	+++		++++
843.		4-(7-(1-methylpiperidin-4-ylamino)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	++++
844.		4-(7-(2-oxo-1,2-dihydropyrimidin-5-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		++++
845.		4-(7-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++

846.		4-(6-bromo-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide		Similar to example 1	++++	++++	++++	++++
847.		4-(6-bromo-8-(quinuclidin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide		Similar to example 1	++++	++++	++++	++++
848.		4-(7-(1,3,5-trimethyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		++++
849.		4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

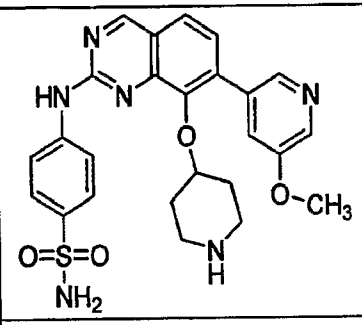
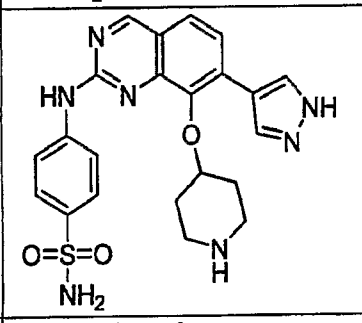
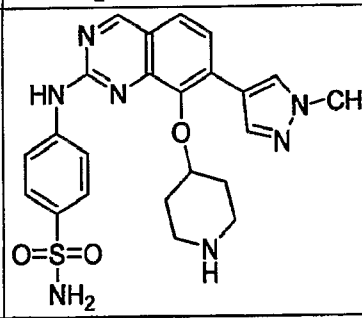
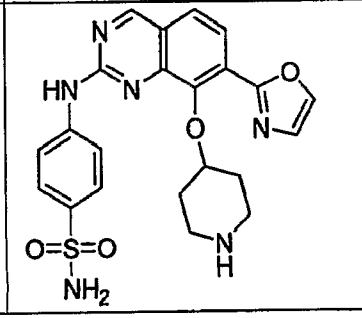
WO 2007/117607 PCT/US2007/008592

850.		4-(7-(2-(2-(pyrrolidin-1-yl)ethylamino)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
851.		4-(7-(2-(pyrrolidin-1-yl)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			+++	++++		
852.		4-(7-(2-morpholinopyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
853.		4-(8-(piperidin-4-yloxy)-7-(pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

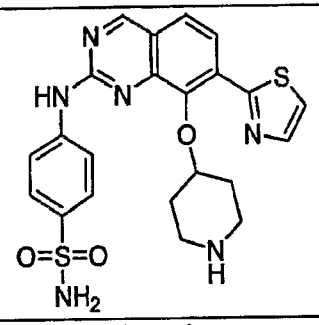
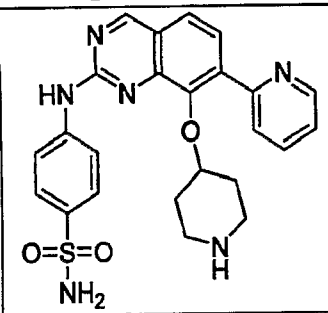
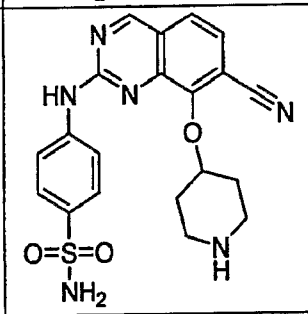
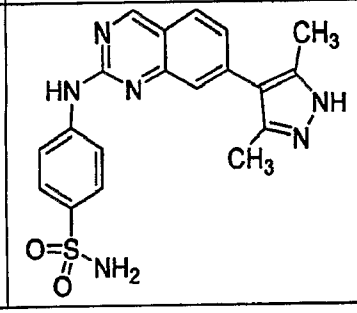
WO 2007/117607 PCT/US2007/008592

854.		4-(8-(piperidin-4-yloxy)-2-(4-sulfamoylphenylamino)quinazolin-7-yl)benzamide			++++	+++		
855.		4-(8-(piperidin-4-yloxy)-7-(pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
856.		4-(7-(6-aminopyridin-3-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
857.		4-(7-(2-aminopyrimidin-5-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		

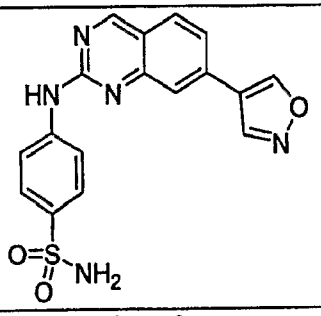
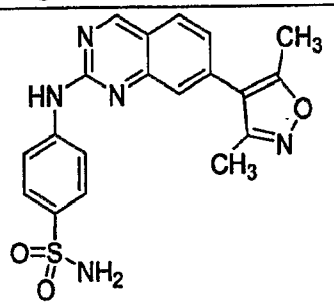
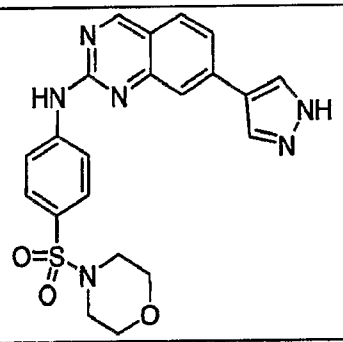
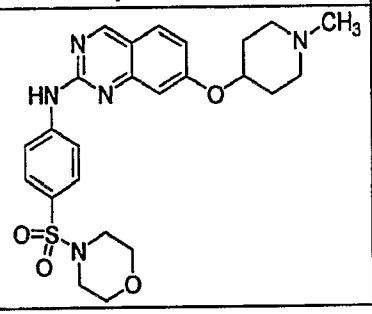
WO 2007/117607 PCT/US2007/008592

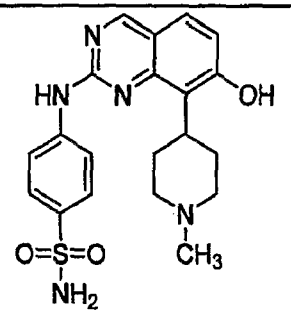
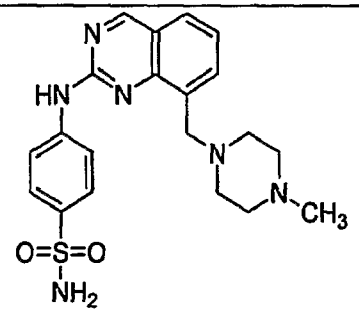
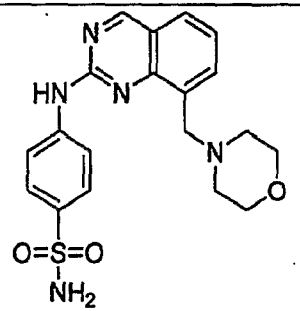
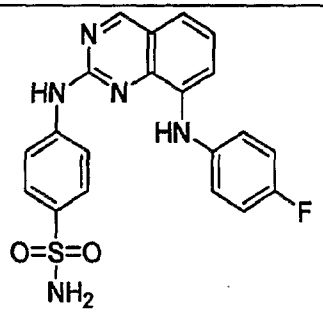
858.		4-(7-(5-methoxypyridin-3-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
859.		4-(8-(piperidin-4-yloxy)-7-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
860.		4-(7-(1-methyl-1H-pyrazol-4-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
861.		4-(7-(oxazol-2-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

WO 2007/117607 PCT/US2007/008592

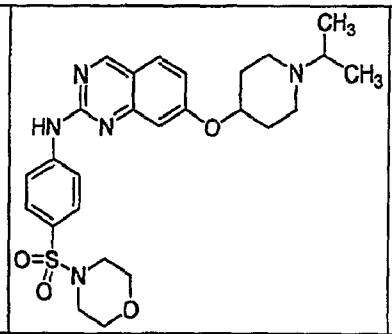
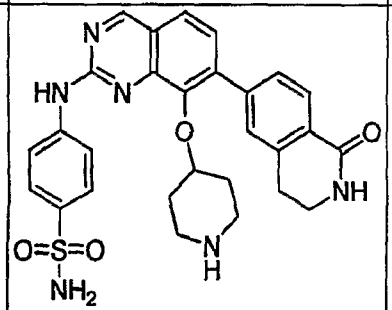
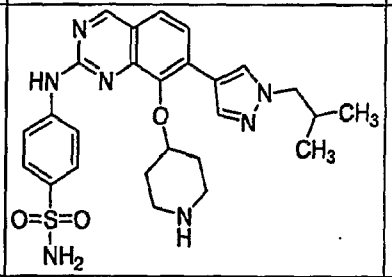
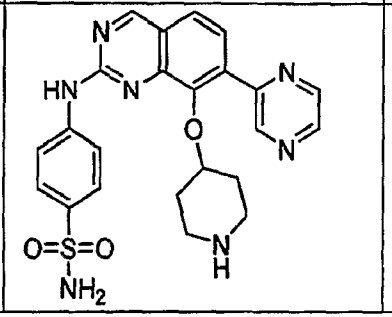
862.		4-(8-(piperidin-4-yloxy)-7-(thiazol-2-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
863.		4-(8-(piperidin-4-yloxy)-7-(pyridin-2-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
864.		4-(7-cyano-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
865.		4-(7-(3,5-dimethyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

WO 2007/117607 PCT/US2007/008592

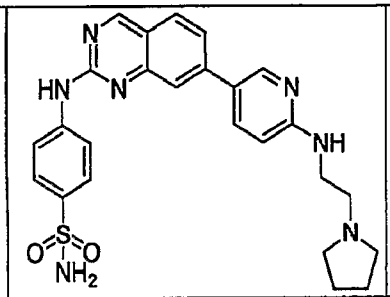
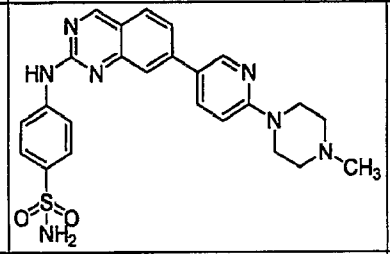
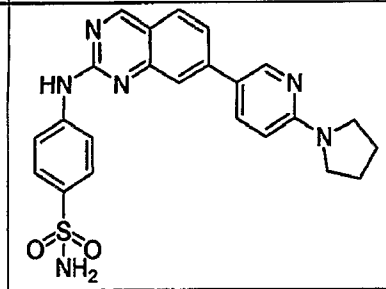
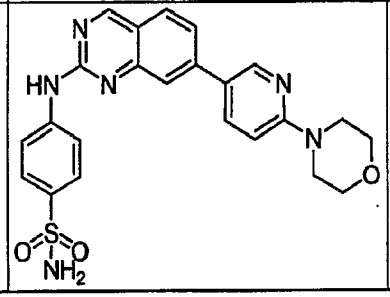
866.		4-(7-(isoxazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
867.		4-(7-(3,5-dimethylisoxazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
868.		N-(4-(morpholinosulfonyl)phenyl)-7-(1H-pyrazol-4-yl)quinazolin-2-amine			++++	++++		
869.		7-(1-methylpiperidin-4-yloxy)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine			++++	++++	++++	

870.		4-(7-hydroxy-8-(1-methylpiperidin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
871.		4-(8-((4-methylpiperazin-1-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
872.		4-(8-(morpholinomethyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
873.		4-(8-(4-fluorophenylamino)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

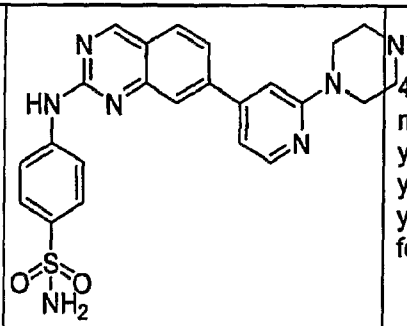
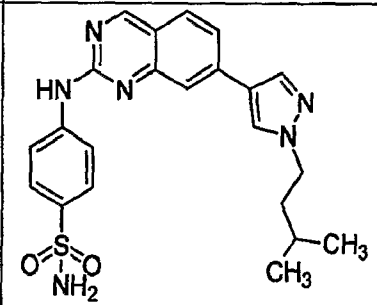
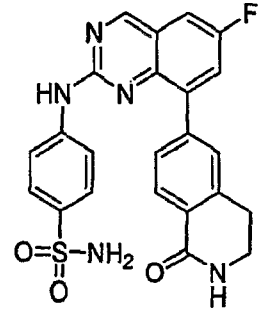
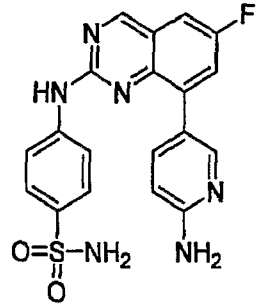
WO 2007/117607 PCT/US2007/008592

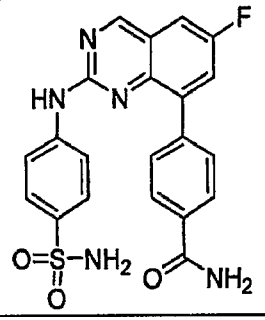
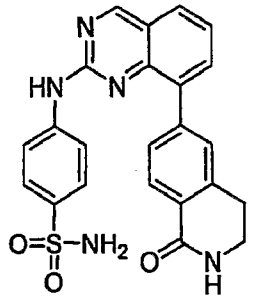
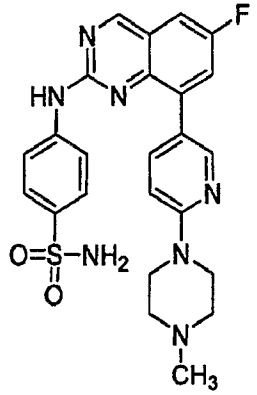
874.		7-(1-isopropylpiperidin-4-yloxy)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine			++++	++++		
875.		4-(7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
876.		4-(7-(1-isobutyl-1H-pyrazol-4-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
877.		4-(8-(piperidin-4-yloxy)-7-(pyrazin-2-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

WO 2007/117607 PCT/US2007/008592

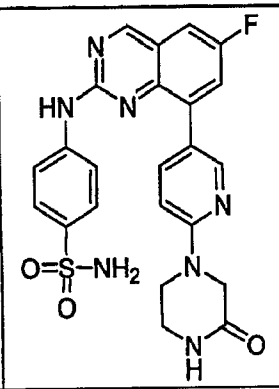
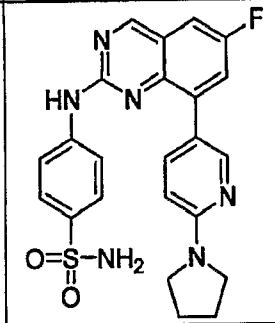
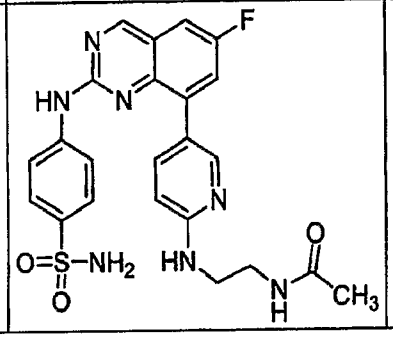
878.		4-(7-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
879.		4-(7-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
880.		4-(7-(6-(pyrrolidin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
881.		4-(7-(6-morpholinopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

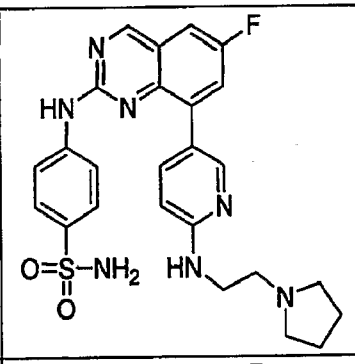
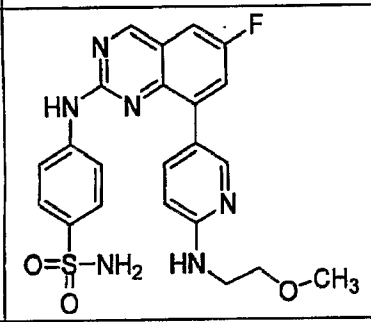
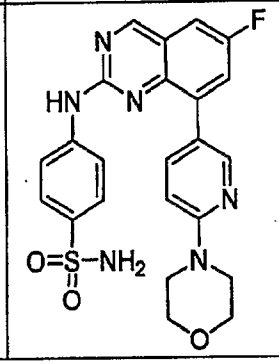
WO 2007/117607 PCT/US2007/008592

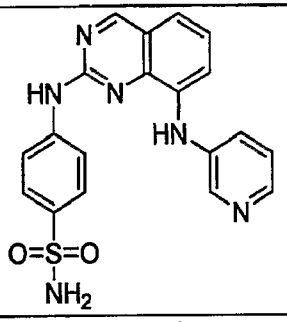
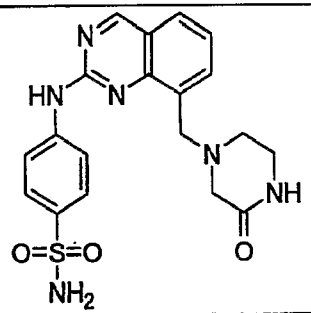
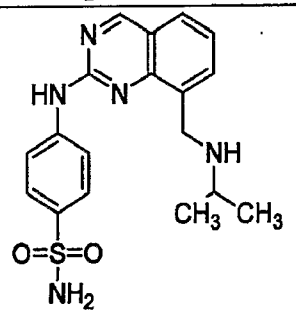
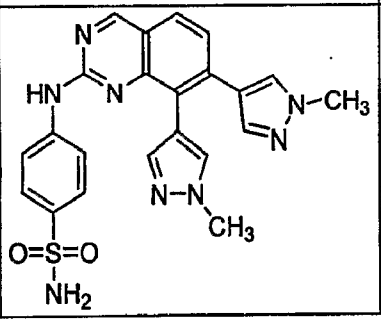
882.		4-(7-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
883.		4-(7-(1-isopentyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
884.		4-(6-fluoro-8-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
885.		4-(8-(6-aminopyridin-3-yl)-6-fluoroquinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	

886.		4-(6-fluoro-2-(4-sulfamoylphenylamino)quinazolin-8-yl)benzamide			++++	+++		
887.		4-(8-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
888.		4-(6-fluoro-8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	

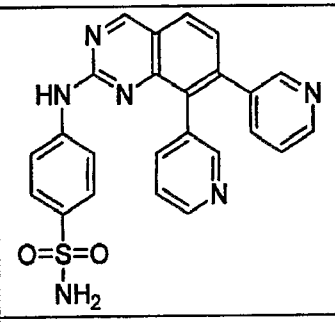
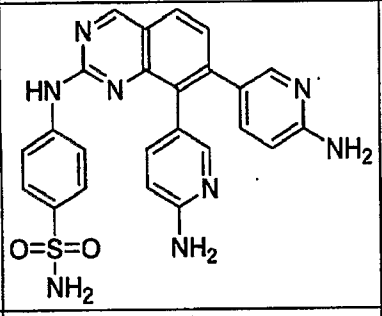
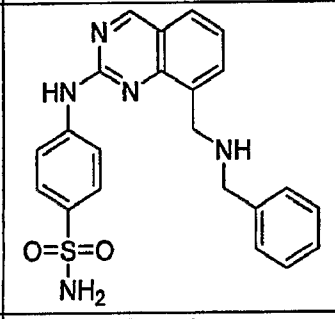
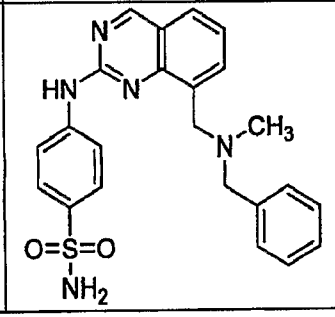
WO 2007/117607 PCT/US2007/008592

889.		4-(6-fluoro-8-(6-(3-oxopiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
890.		4-(6-fluoro-8-(6-(pyrrolidin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
891.		N-(2-(5-(6-fluoro-2-(4-sulfamoylphenylamino)quinazolin-8-yl)pyridin-2-ylamino)ethyl)acetamide			++++	++++		

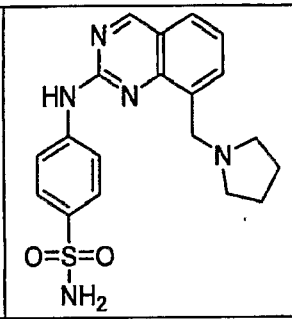
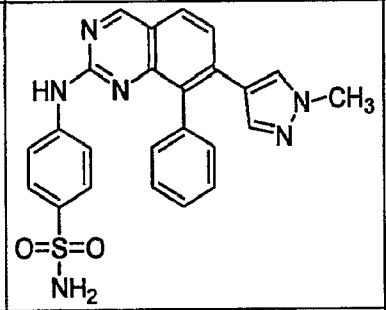
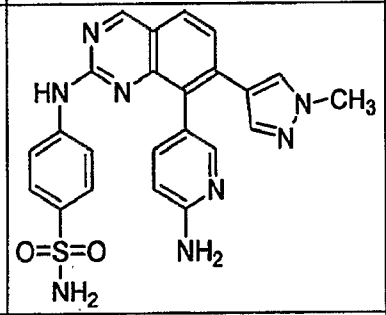
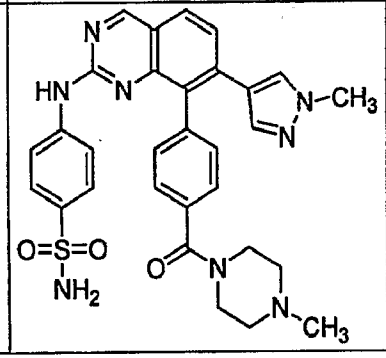
892.		4-(6-fluoro-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
893.		4-(6-fluoro-8-(6-(2-methoxyethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
894.		4-(6-fluoro-8-(6-morpholinopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	

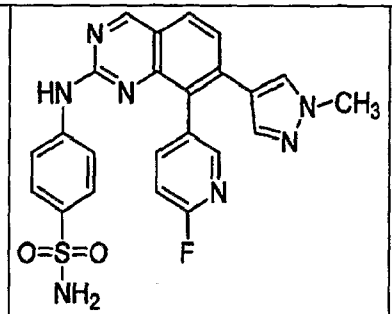
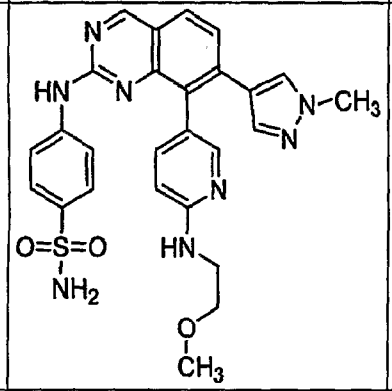
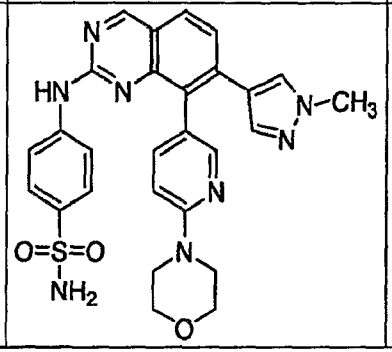
895.		4-(8-(pyridin-3-ylamino)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
896.		4-(8-((3-oxopiperazin-1-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
897.		4-(8-((isopropylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
898.		4-(7,8-bis(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

WO 2007/117607 PCT/US2007/008592

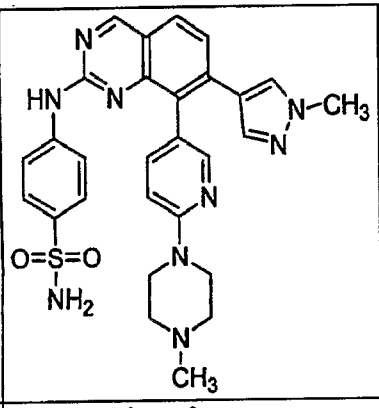
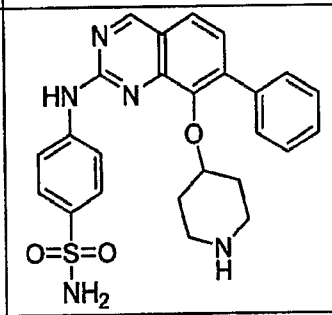
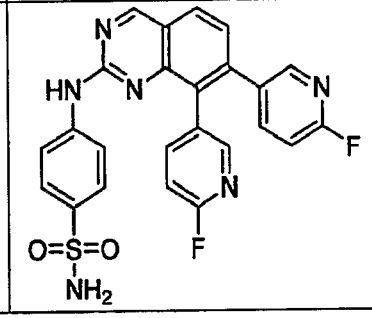
899.		4-(7,8-di(pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
900.		4-(7,8-bis(6-aminopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
901.		4-(8-((benzylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
902.		4-(8-((benzylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

WO 2007/117607 PCT/US2007/008592

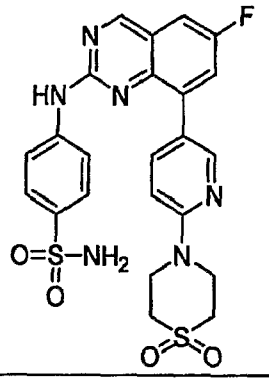
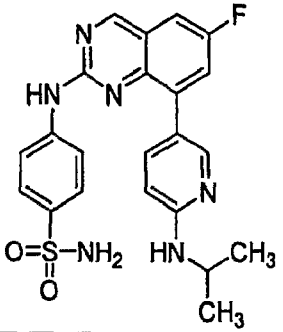
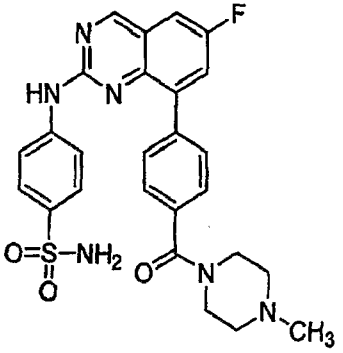
903.		4-(8-(pyrrolidin-1-ylmethyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
904.		4-(7-(1-methyl-1H-pyrazol-4-yl)-8-phenylquinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
905.		4-(8-(6-aminopyridin-3-yl)-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
906.		4-(7-(1-methyl-1H-pyrazol-4-yl)-8-(4-(4-methylpiperazine-1-carbonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	

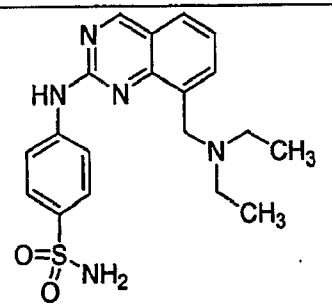
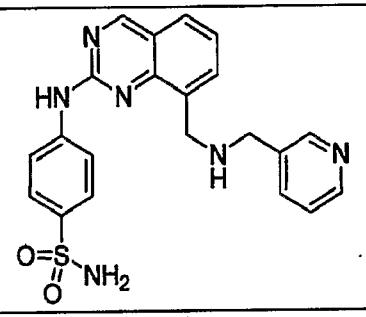
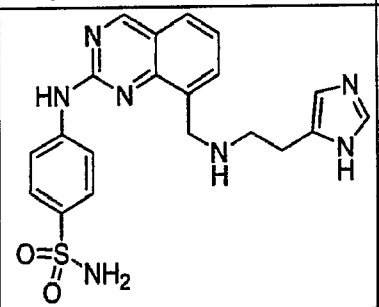
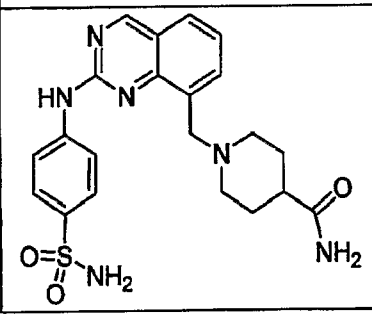
907.		4-(8-(6-fluoropyridin-3-yl)-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
908.		4-(8-(6-(2-methoxyethylamino)pyridin-3-yl)-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
909.		4-(7-(1-methyl-1H-pyrazol-4-yl)-8-(6-morpholinopyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	

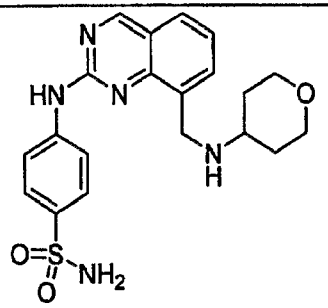
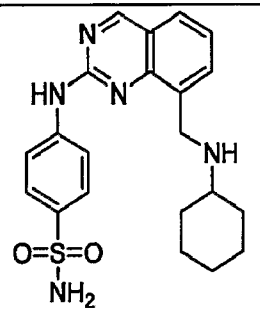
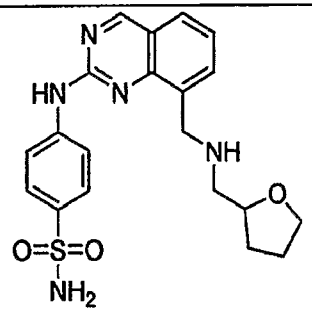
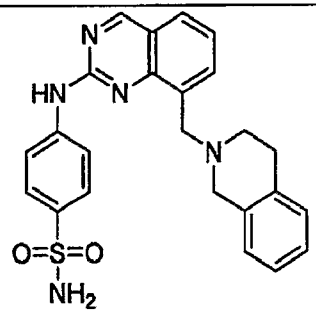
WO 2007/117607 PCT/US2007/008592

910.		4-(7-(1-methyl-1H-pyrazol-4-yl)-8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
911.		4-(7-phenyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
912.		4-(7,8-bis(6-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

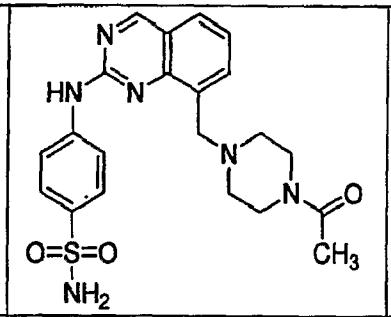
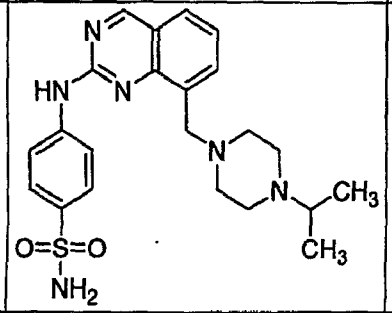
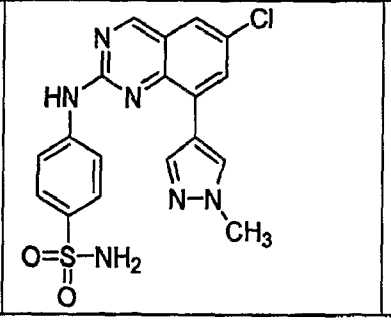
WO 2007/117607 PCT/US2007/008592

913.					++++	++++	++++	
914.		4-(6-fluoro-8-(6-(isopropylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	
915.		4-(6-fluoro-8-(4-(4-methylpiperazine-1-carbonyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	++++	

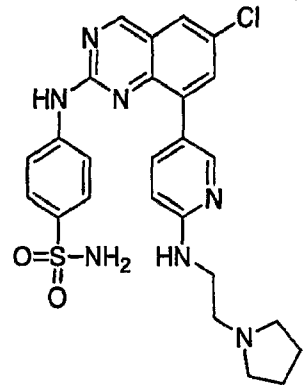
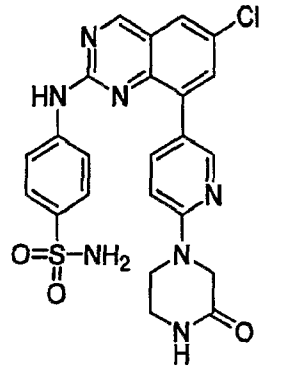
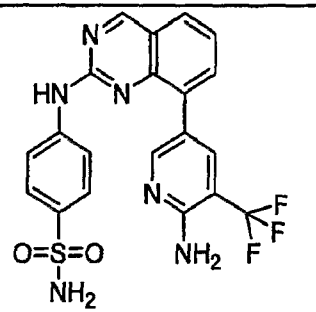
916.		4-(8-((diethylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
917.		4-(8-((pyridin-3-ylmethylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
918.		4-(8-((2-(1H-imidazol-5-yl)ethylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	+++		
919.		1-((2-(4-sulfamoylphenylamino)quinazolin-8-yl)methyl)piperidine-4-carboxamide			++++	+++		

920.		4-(8-((tetrahydro-2H-pyran-4-ylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
921.		4-(8-((cyclohexylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
922.		4-(8-(((tetrahydrofuran-2-yl)methylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
923.		4-(8-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		

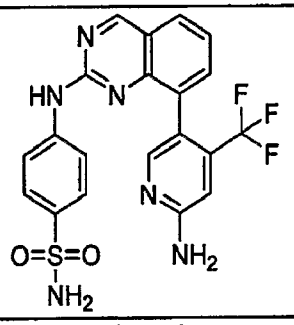
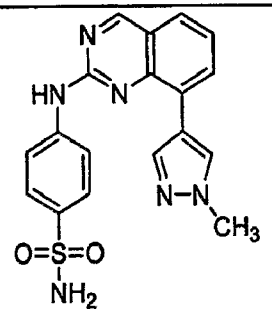
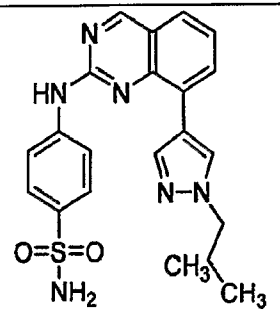
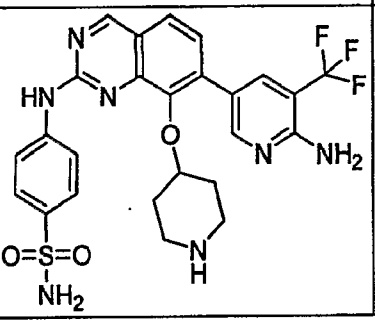
WO 2007/117607 PCT/US2007/008592

924.		4-(8-((4-acetylpiperazin-1-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++		
925.		4-(8-((4-isopropylpiperazin-1-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++	++++	+++	
926.		4-(6-chloro-8-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

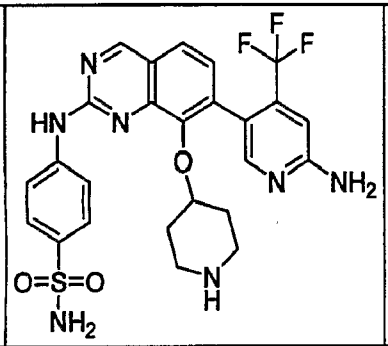
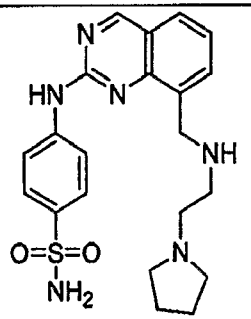
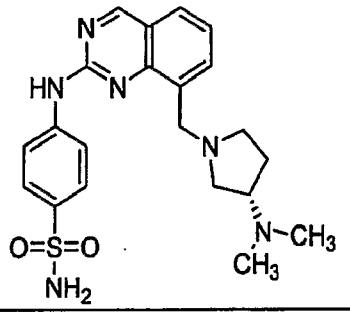
WO 2007/117607 PCT/US2007/008592

927.		4-(6-chloro-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
928.		4-(6-chloro-8-(6-(3-methylenepiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
929.		4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

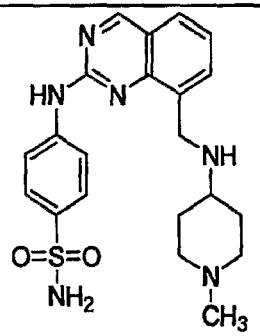
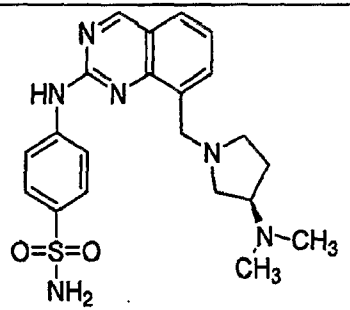
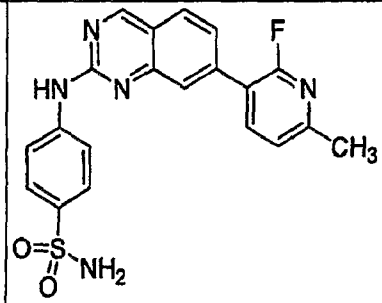
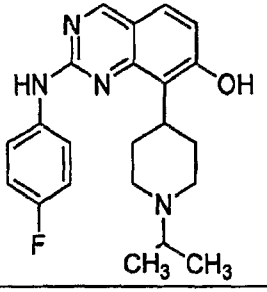
WO 2007/117607 PCT/US2007/008592

930.		4-(8-(6-amino-4-(trifluoromethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
931.		4-(8-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
932.		(E)-4-(2-(2-(1-isobutyl-1H-pyrazol-4-yl)phenyl)guanidino)benzenesulfonamide			++++		++++	
933.		4-(7-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

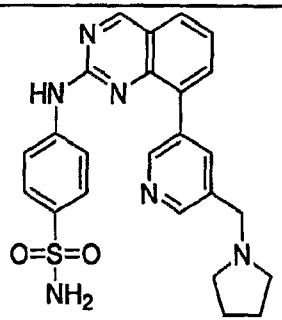
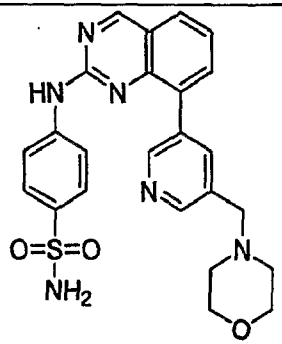
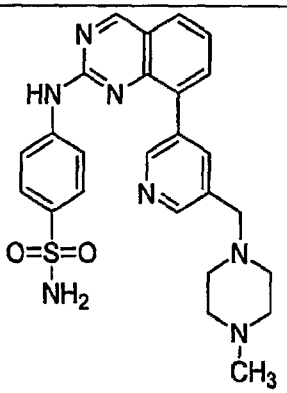
WO 2007/117607 PCT/US2007/008592

934.		4-(7-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
935.		4-(8-((2-(pyrrolidin-1-yl)ethylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
936.		(S)-4-(8-((3-(dimethylamino)pyrrolidin-1-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

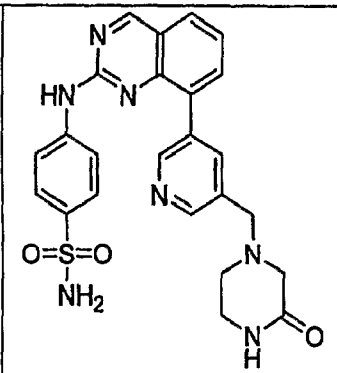
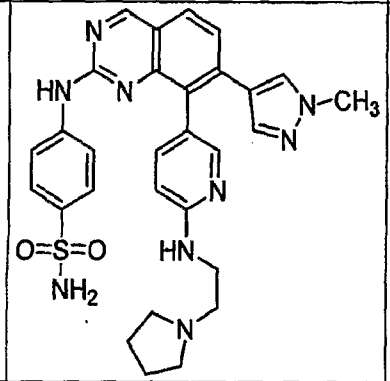
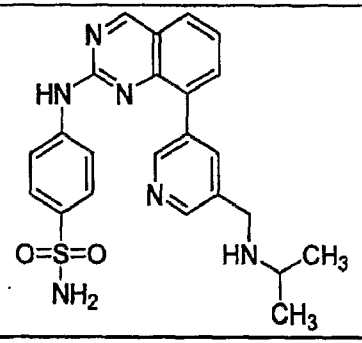
WO 2007/117607 PCT/US2007/008592

937.		4-(8-((1-methylpiperidin-4-ylamino)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
938.		(R)-4-(8-((3-(dimethylamino)pyrrolidin-1-yl)methyl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
939.		4-(7-(2-fluoro-6-methylpyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
940.		2-(4-fluorophenylamino)-8-(1-isopropylpiperidin-4-yl)quinazolin-7-ol			++++		+++	

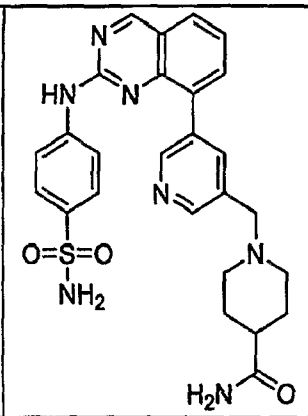
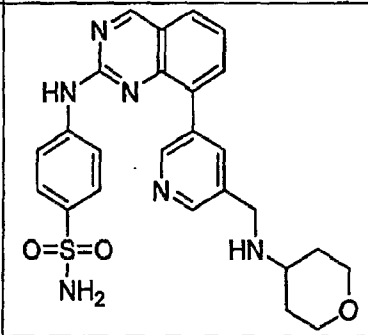
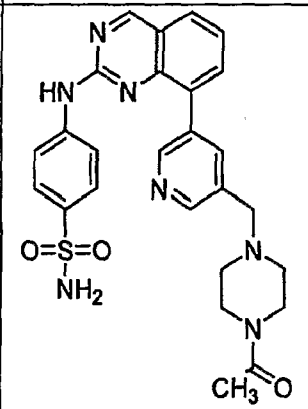
WO 2007/117607 PCT/US2007/008592

941.		4-(8-(5-(pyrrolidin-1-ylmethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
942.		4-(8-(5-(morpholinomethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
943.		4-(8-(5-((4-methylpiperazin-1-yl)methyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

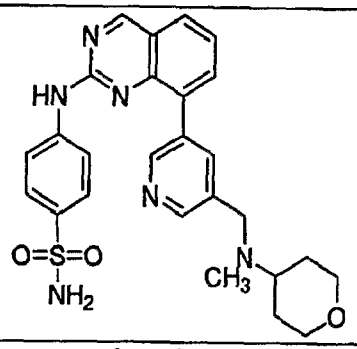
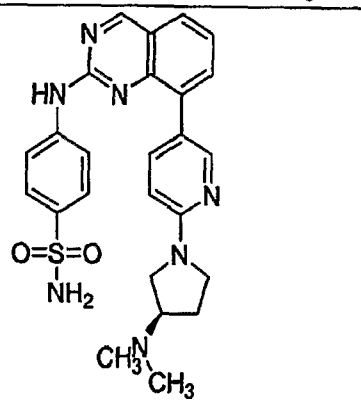
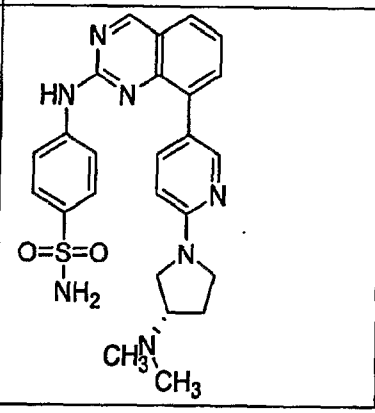
WO 2007/117607 PCT/US2007/008592

944.		4-(8-(5-((3-oxopiperazin-1-yl)methyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
945.		4-(7-(1-methyl-1H-pyrazol-4-yl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
946.		4-(8-(5-((isopropylamino)methyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

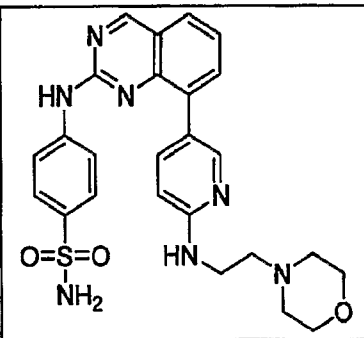
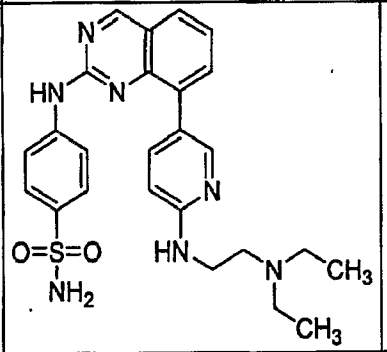
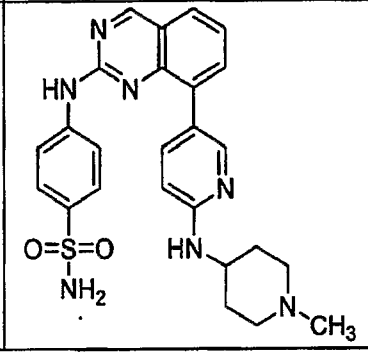
WO 2007/117607 PCT/US2007/008592

947.		1-((5-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)pyridin-3-yl)methyl)piperidine-4-carboxamide			++++		+++	
948.		4-(8-(5-((tetrahydro-2H-pyran-4-ylamino)methyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
949.		4-(8-(5-((4-acetylpiperazin-1-yl)methyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	

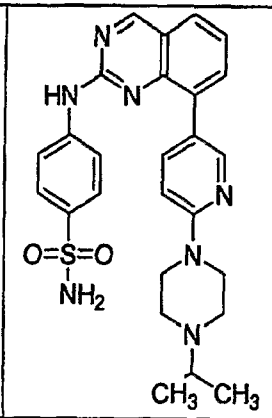
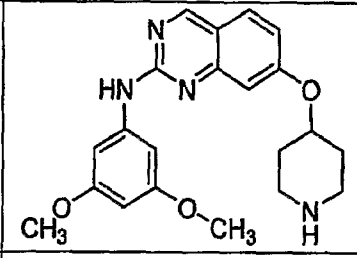
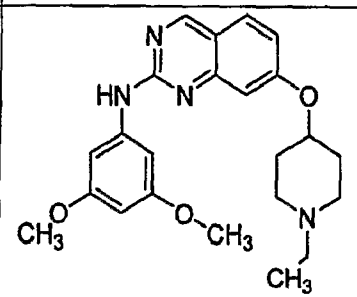
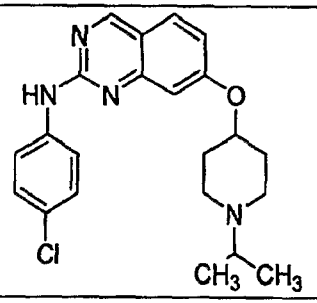
WO 2007/117607 PCT/US2007/008592

950.		4-(8-(5-((methyl(tetrahydro-2H-pyran-4-yl)amino)methyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
951.		(R)-4-(8-(6-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
952.		(S)-4-(8-(6-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

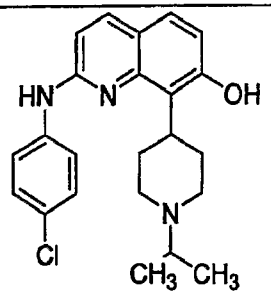
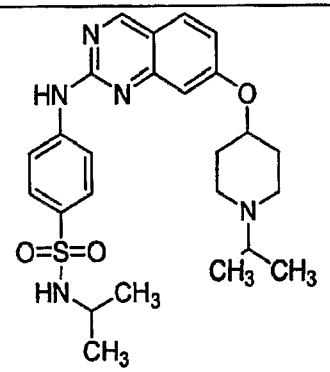
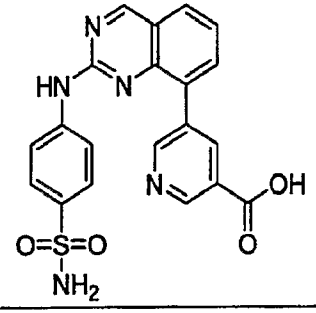
WO 2007/117607 PCT/US2007/008592

953.		4-(8-(6-(2-morpholinoethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
954.		4-(8-(6-(2-(diethylamino)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
955.		4-(8-(6-(1-methylpiperidin-4-ylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

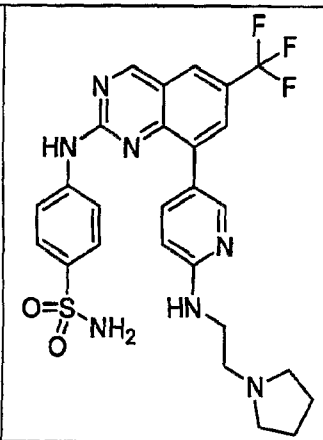
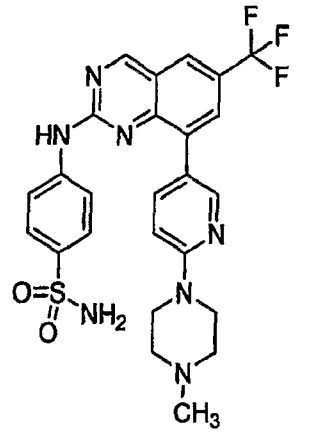
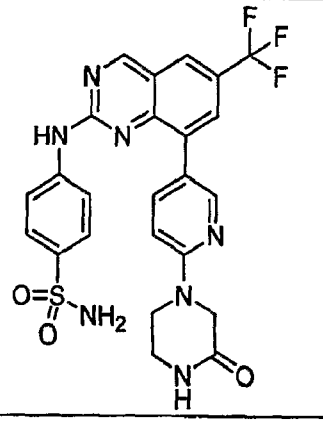
WO 2007/117607 PCT/US2007/008592

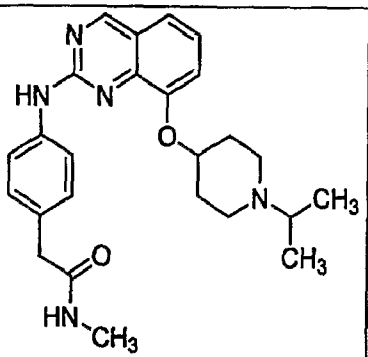
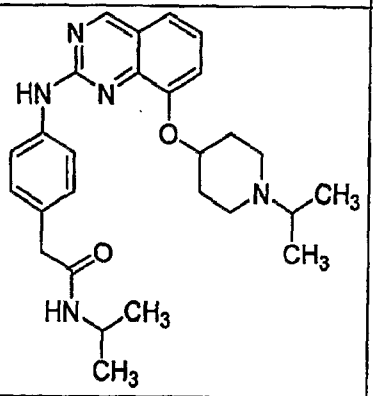
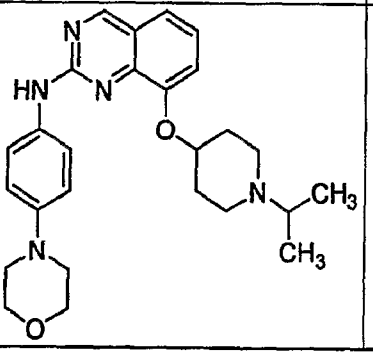
956.		4-(8-(6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
957.		N-(3,5-dimethoxyphenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine			++++		++++	
958.		N-(3,5-dimethoxyphenyl)-7-(1-ethylpiperidin-4-yloxy)quinazolin-2-amine			++++		++++	
959.		N-(4-chlorophenyl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine			++++		++++	

WO 2007/117607 PCT/US2007/008592

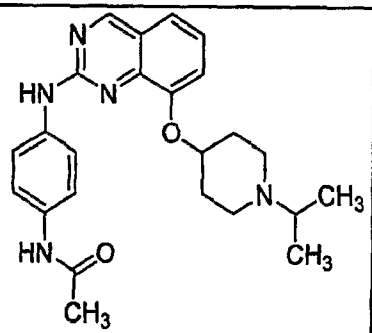
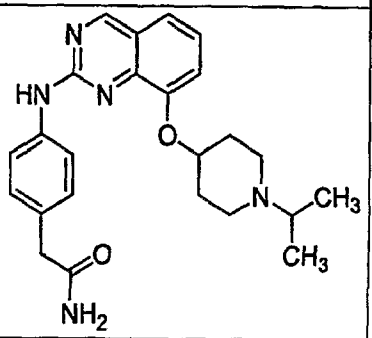
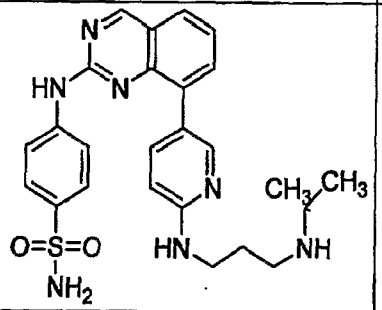
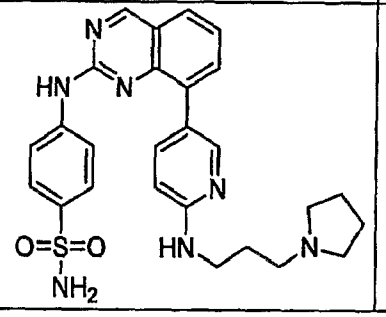
960.		2-(4-chlorophenylamino)-8-(1-isopropylpiperidin-4-yl)quinolin-7-ol			++++		+++	
961.		N-isopropyl-4-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
962.		5-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)nicotinic acid			+++		+++	

WO 2007/117607 PCT/US2007/008592

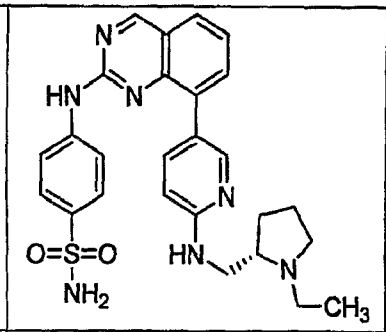
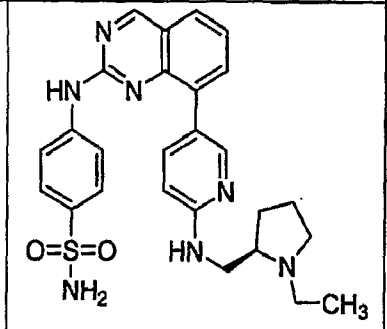
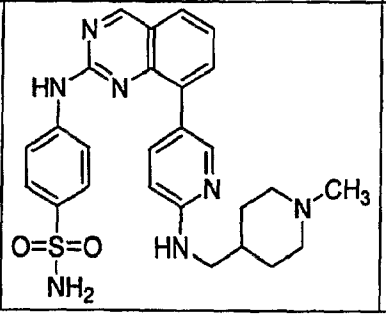
963.		4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide		Example 17	++++		++++	
964.		4-(8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide		Example 17, using N-methylpiperazine in place of 1-(2-aminoethyl)pyrrolidine	+++		++++	
965.		4-(8-(6-(3-oxopiperazin-1-yl)pyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide		Example 17, using piperazin-2-one in place of 1-(2-aminoethyl)pyrrolidine	++++		++++	

966.		2-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-methylacetamide	544.1, 2.16	Example 18	++++		++++	
967.		N-isopropyl-2-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide		Example 18 step 2, using 2-(4-aminophenyl)-N-isopropylacetamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
968.		8-(1-isopropylpiperidin-4-yloxy)-N-(4-morpholinophenyl)quinazolin-2-amine		Example 18 step 2, using 4-morpholinoaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	

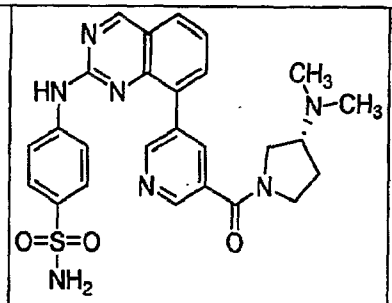
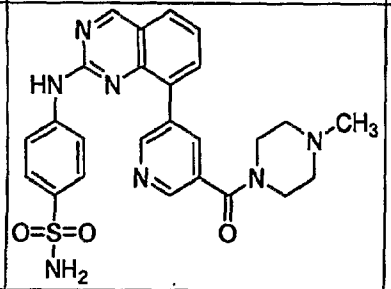
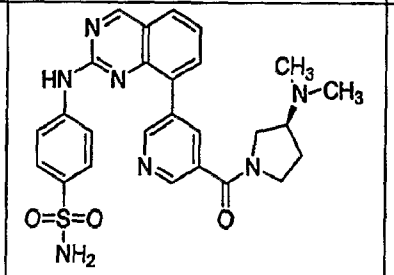
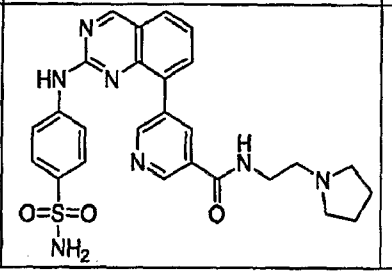
WO 2007/117607 PCT/US2007/008592

969.		N-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide		Example 18 step 2, using 4-aminoacetanilide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
970.		2-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide		Example 18 step 2, using 2-(4-aminophenyl)acetamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
971.		4-(8-(6-(3-(isopropylamino)propylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
972.		4-(8-(6-(3-(pyrrolidin-1-yl)propylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

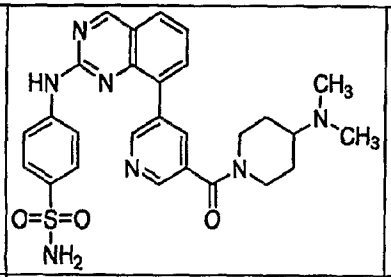
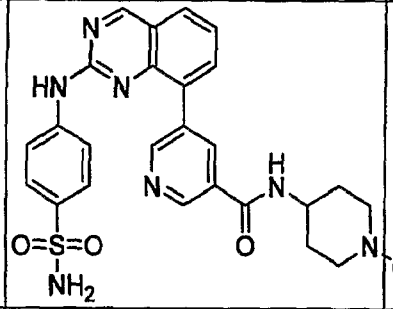
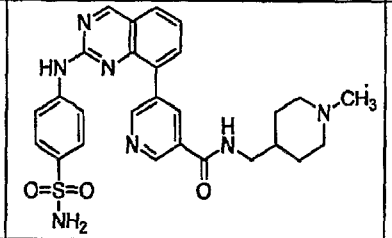
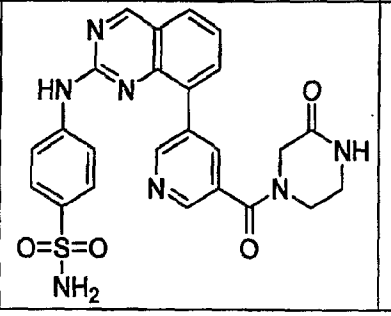
WO 2007/117607 PCT/US2007/008592

973.		(S)-4-(8-(6-((1-ethylpyrrolidin-2-yl)methylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
974.		(R)-4-(8-(6-((1-ethylpyrrolidin-2-yl)methylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
975.		4-(8-(6-((1-methylpiperidin-4-yl)methylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

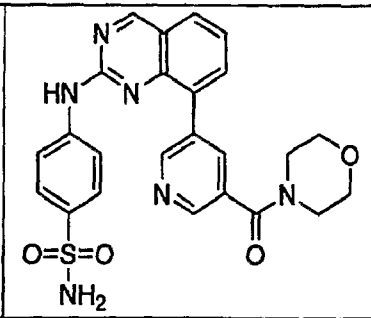
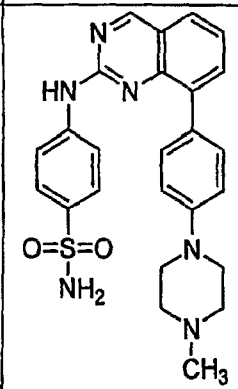
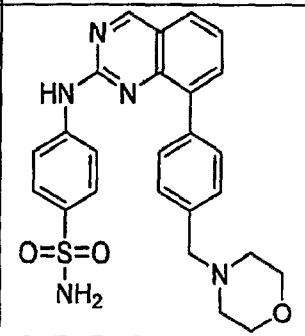
WO 2007/117607 PCT/US2007/008592

976.		(R)-4-(8-(5-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
977.		4-(8-(5-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
978.		(S)-4-(8-(5-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
979.		N-(2-(pyrrolidin-1-yl)ethyl)-5-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)nicotinamide			++++		+++	

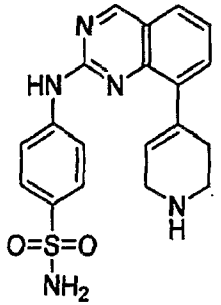
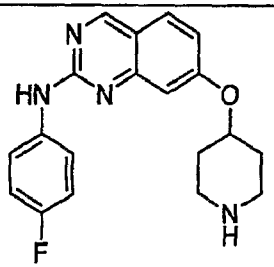
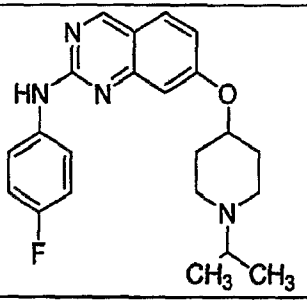
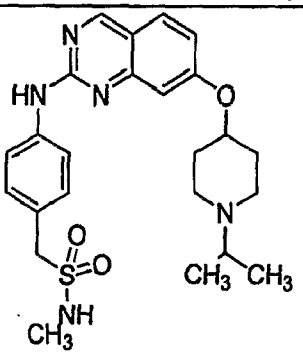
WO 2007/117607 PCT/US2007/008592

980.		4-(8-(5-(4-(dimethylamino)piperidine-1-carbonyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
981.		N-(1-methylpiperidin-4-yl)-5-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)nicotinamide			++++		+++	
982.		N-((1-methylpiperidin-4-yl)methyl)-5-(2-(4-sulfamoylphenylamino)quinazolin-8-yl)nicotinamide			++++		+++	
983.		4-(8-(5-(3-oxopiperazine-1-carbonyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	

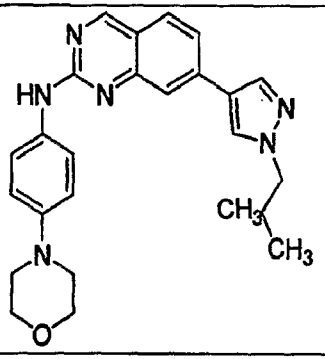
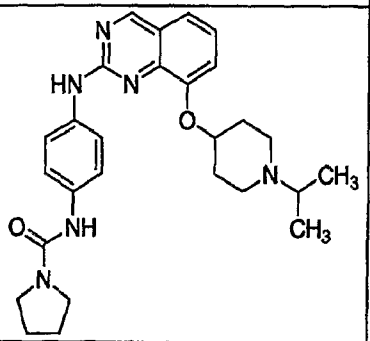
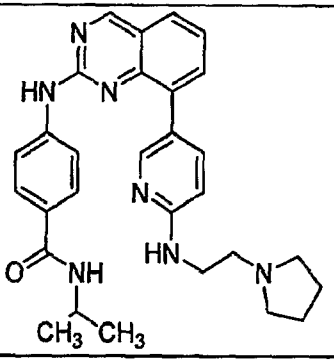
WO 2007/117607 PCT/US2007/008592

984.		4-(8-(5-(morpholine-4-carbonyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		+++	
985.		4-(8-(4-(4-methylpiperazin-1-yl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
986.		4-(8-(4-(morpholinomethyl)phenyl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

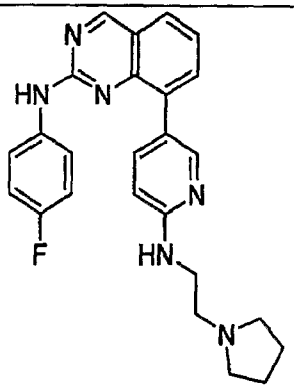
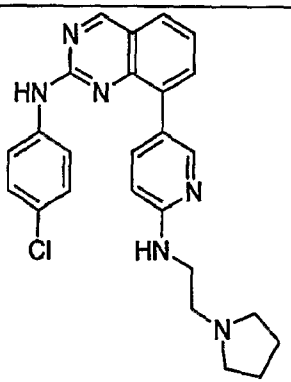
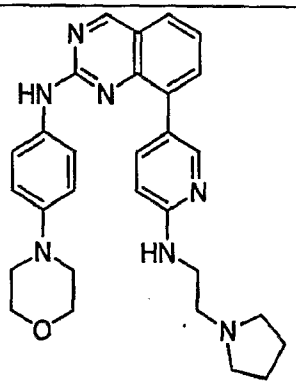
WO 2007/117607 PCT/US2007/008592

987.		4-(8-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	
988.		N-(4-fluorophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine			++++		++++	
989.		N-(4-fluorophenyl)-7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine			++++		+++	
990.		1-(4-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-methylmethanesulfonamide			++++		++++	

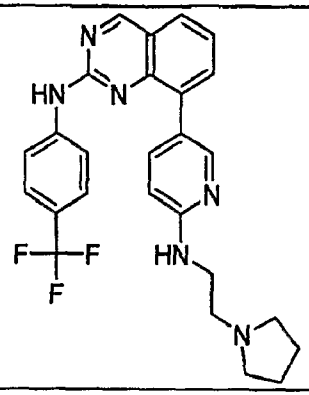
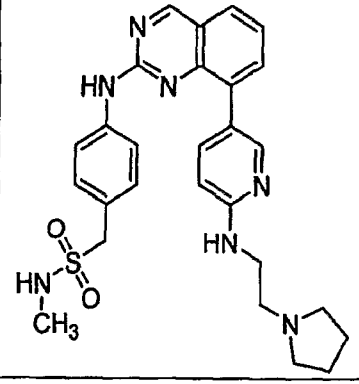
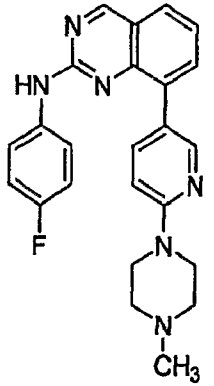
WO 2007/117607 PCT/US2007/008592

991.		7-(1-isobutyl-1H-pyrazol-4-yl)-N-(4-morpholinophenyl)quinazolin-2-amine			++++		++++	
992.		N-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)pyrrolidine-1-carboxamide		Example 13, using 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in place of 2-chloro-8-methoxyquinazoline and N-(4-aminophenyl)pyrrolidine-1-carboxamide in place of 3,5-dimethoxyaniline	++++		++++	
993.		N-isopropyl-4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzamide			++++		++++	

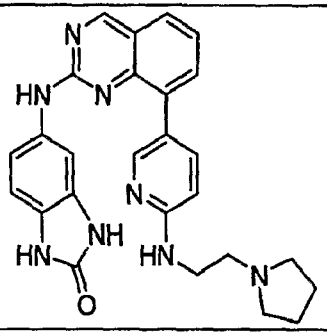
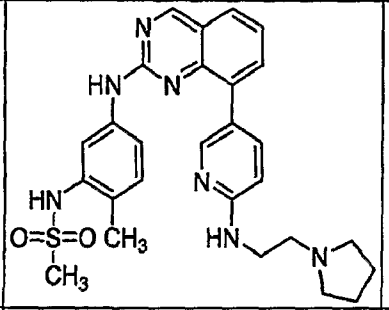
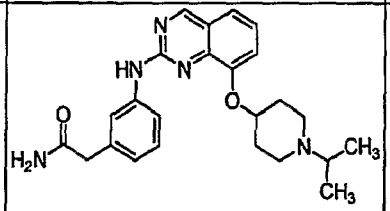
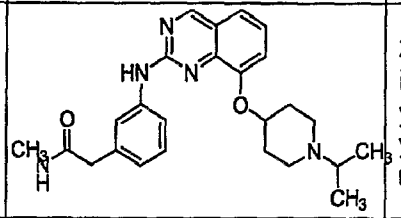
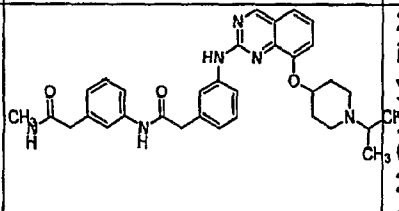
WO 2007/117607 PCT/US2007/008592

994.		N-(4-fluorophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	
995.		N-(4-chlorophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	
996.		N-(4-morpholinophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	

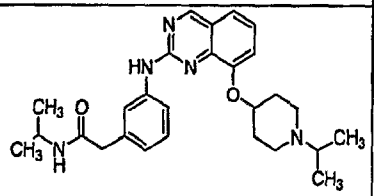
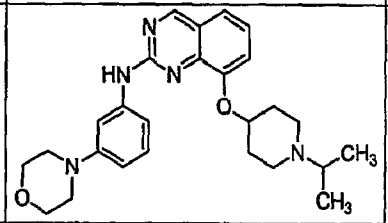
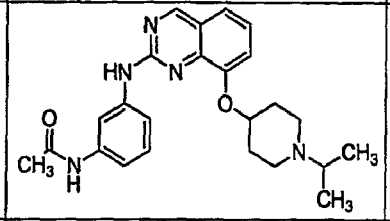
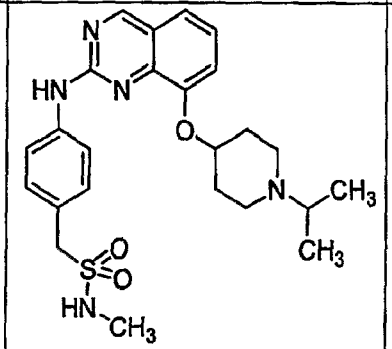
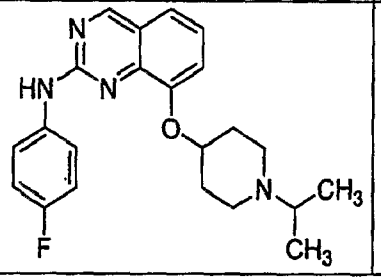
WO 2007/117607 PCT/US2007/008592

997.		8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-N-(4-(trifluoromethyl)phenyl)quinazolin-2-amine			++++		++++	
998.		N-methyl-1-(4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)methanesulfonamide			++++		++++	
999.		N-(4-fluorophenyl)-8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)quinazolin-2-amine			++++		++++	

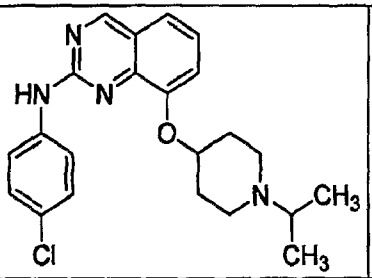
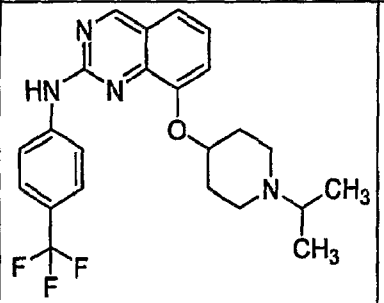
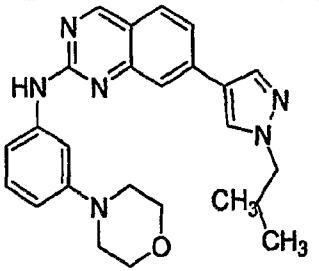
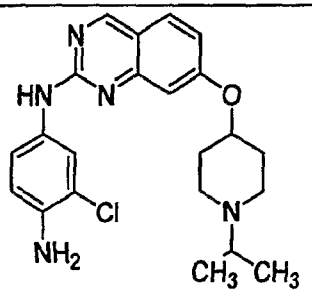
WO 2007/117607 PCT/US2007/008592

1000.		5-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)-1H-benzo[d]imidazol-2(3H)-one			++++		++++	
1001.		N-(2-methyl-5-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)methanesulfonamide			++++		++++	
1002.		2-(3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide		Example 18 step 2, using 2-(3-aminophenyl)acetamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		+++	
1003.		2-(3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-methylacetamide		Example 18 step 2, using 2-(3-aminophenyl)-N-methylacetamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
1004.		2-(3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-(3-(2-(methylamino)-2-oxoethyl)phenyl)acetamide		Example 18 step 2, using 2-(4-aminophenyl)-N-(3-(2-(methylamino)-2-oxoethyl)phenyl)acetamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	

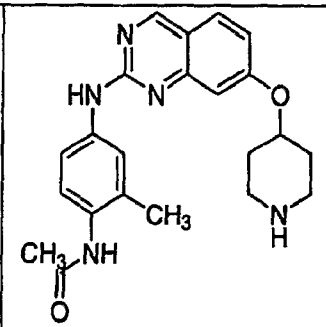
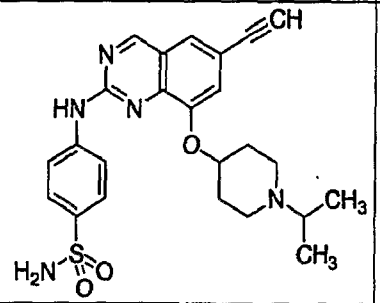
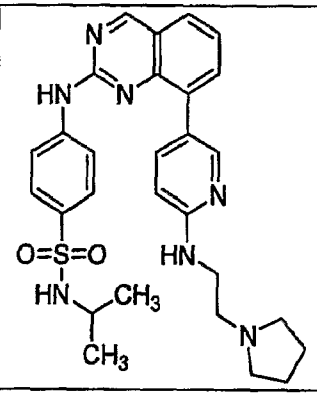
WO 2007/117607 PCT/US2007/008592

		tamide						
1005.		N-isopropyl-2-(3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide		Example 18 step 2, using 2-(3-aminophenyl)-N-isopropylacetamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
1006.		8-(1-isopropylpiperidin-4-yloxy)-N-(3-morpholinophenyl)quinazolin-2-amine		Example 18 step 2, using 3-morpholinoaniline in place of 2-(4-aminophenyl)-N-methylacetamide	++++		+++	
1007.		N-(3-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide		Example 18 step 2, using 3-aminoacetanilide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
1008.		1-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-methylmethanesulfonamide		Example 18 step 2, using 1-(4-aminophenyl)-N-methylmethanesulfonamide in place of 2-(4-aminophenyl)-N-methylacetamide	++++		++++	
1009.		N-(4-fluorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine		Example 13, using 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in place of 2-chloro-8-methoxyquinazoline and 4-fluoroaniline in place of 3,5-dimethoxyaniline	++++		+++	

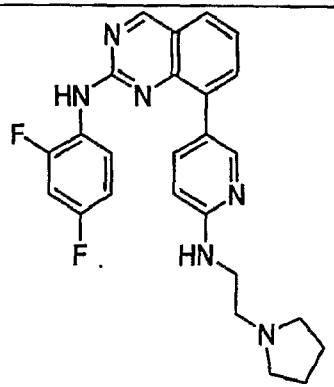
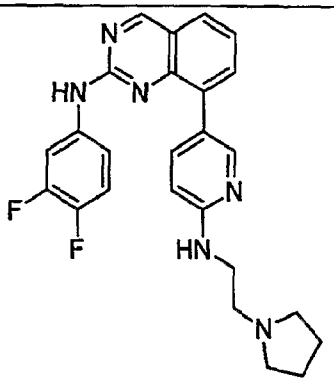
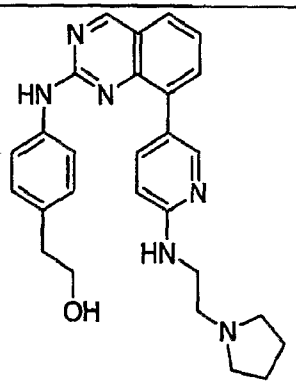
WO 2007/117607 PCT/US2007/008592

1010.		N-(4-chlorophenyl)-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine		Example 13, using 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in place of 2-chloro-8-methoxyquinazoline and 4-chloroaniline in place of 3,5-*dimethoxyaniline*	++++		++++	
1011.		8-(1-isopropylpiperidin-4-yloxy)-N-(4-(trifluoromethyl)phenyl)quinazolin-2-amine		Example 13, using 2-chloro-8-(1-isopropylpiperidin-4-yloxy)*quinazoline* in place of 2-chloro-8-methoxyquinazoline and 4-trifluoromethylaniline in place of 3,5-dimethoxyaniline	++++		++++	
1012.		7-(1-isobutyl-1H-pyrazol-4-yl)-N-(3-morpholinophenyl)quinazolin-2-amine			++++		++++	
1013.		3-chloro-N1-(7-(1-isopropylpiperidin-4-yloxy)quinazolin-2-yl)benzene-1,4-diamine			++++		+++	

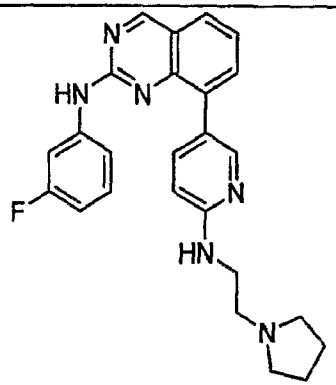
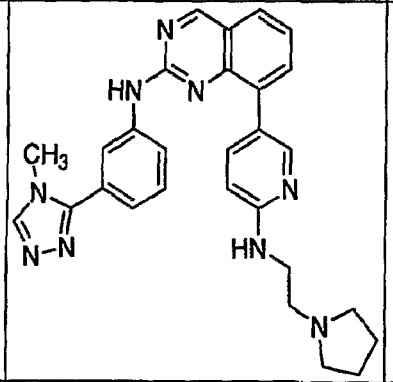
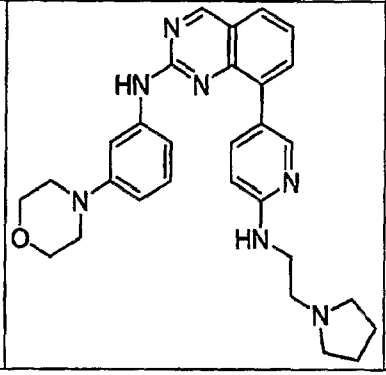
WO 2007/117607 PCT/US2007/008592

1014.		N-(2-methyl-4-(7-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)acetamide			++++		++++	
1015.		4-(6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide		Example 9	++++		++++	
1016.		N-isopropyl-4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide			++++		++++	

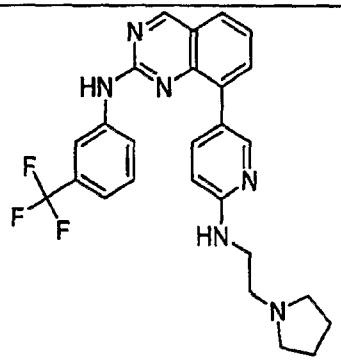
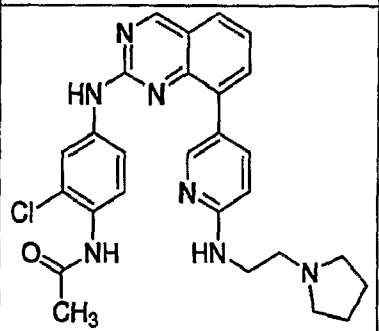
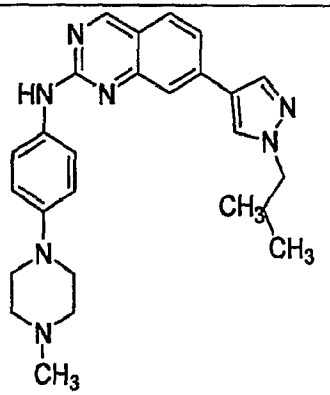
WO 2007/117607 PCT/US2007/008592

1017.		N-(2,4-difluorophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	
1018.		N-(3,4-difluorophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	
1019.		2-(4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)ethanol			++++		++++	

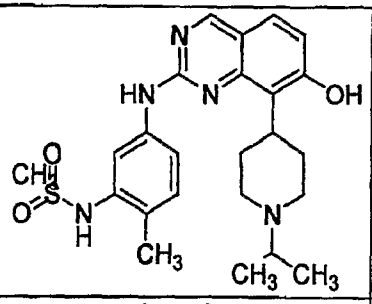
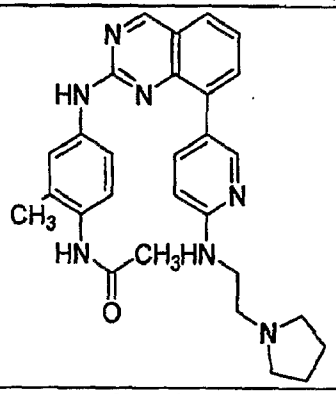
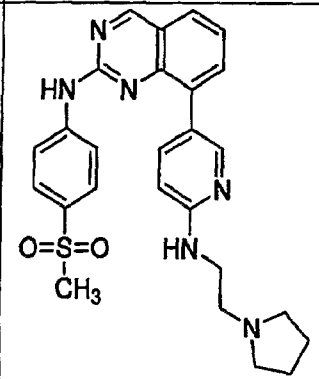
WO 2007/117607 PCT/US2007/008592

1020.		N-(3-fluorophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	
1021.		N-(3-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	
1022.		N-(3-morpholinophenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		++++	

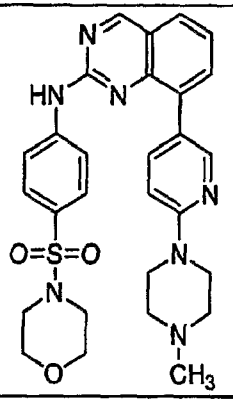
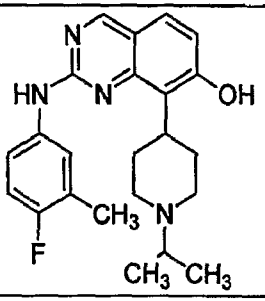
WO 2007/117607 PCT/US2007/008592

1023.		8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine			++++		++++	
1024.		N-(2-chloro-4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide			++++		++++	
1025.		7-(1-isobutyl-1H-pyrazol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)quinazolin-2-amine			++++		++++	

WO 2007/117607 PCT/US2007/008592

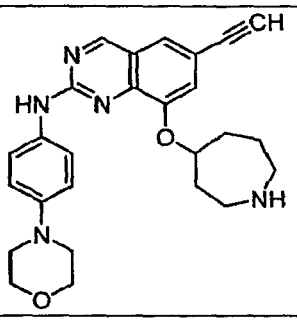
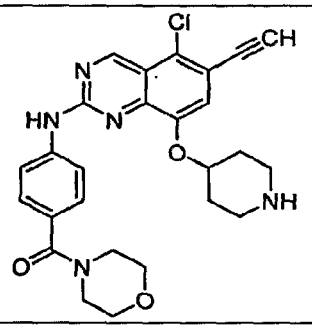
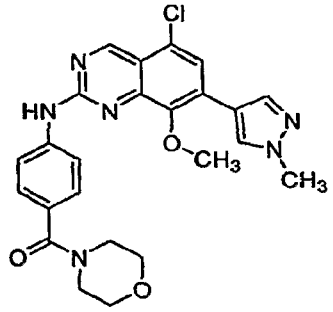
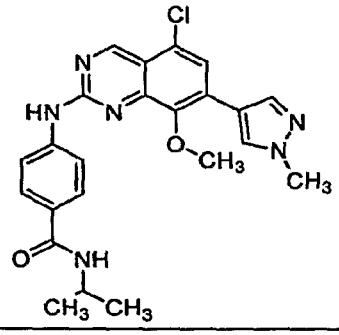
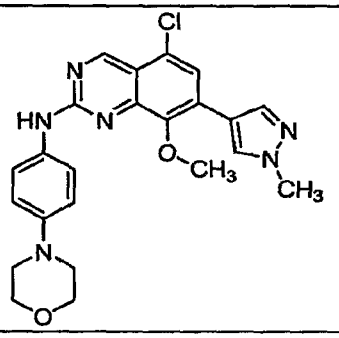
1026.		N-(5-(7-hydroxy-8-(1-isopropylpiperidin-4-yl)quinazolin-2-ylamino)-2-methylphenyl)methanesulfonamide			++++		++++	
1027.		N-(2-methyl-4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide			++++		++++	
1028.		N-(4-(methylsulfonyl)phenyl)-8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)quinazolin-2-amine			++++		+++	

WO 2007/117607 PCT/US2007/008592

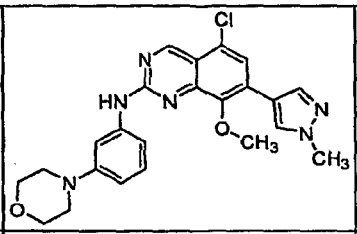
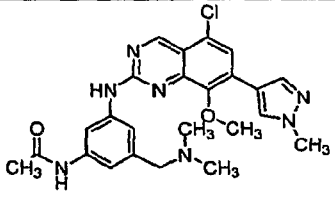
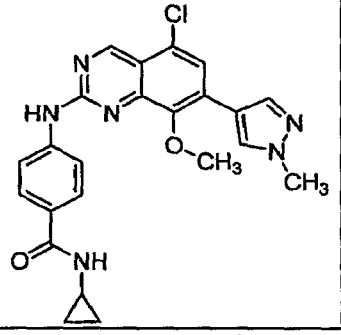
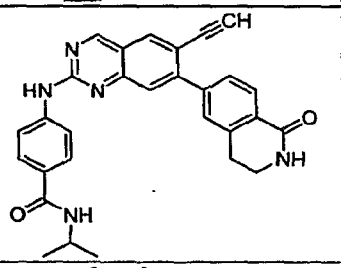
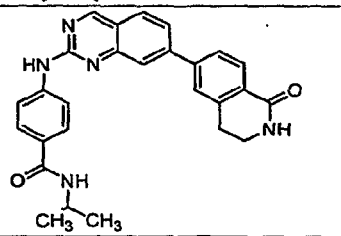
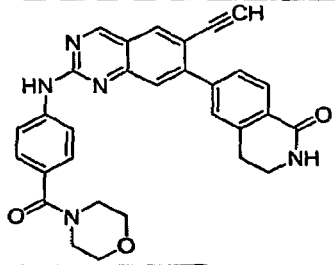
1029.		8-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-N-(4-(morpholinosulfonyl)phenyl)quinazolin-2-amine			++++		++++	
1030.		2-(4-fluoro-3-methylphenylamino)-8-(1-isopropylpiperidin-4-yl)quinazolin-7-ol			++++		+++	

WO 2007/117607 PCT/US2007/008592

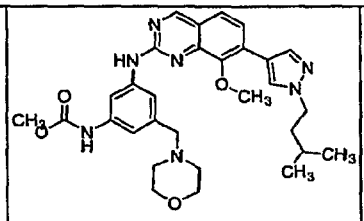
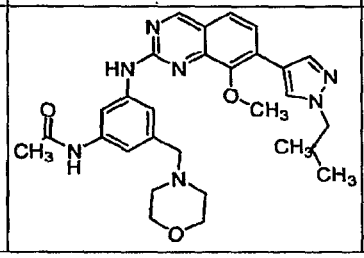
PP028218.0002 (20366-156WO1) **Table 5**

Cmpd	Structure	Name	LC/MS (M+1(m/z), Rt(min))	PDK1 BV11 26 1	CPEC 50 A278 0	CPEC 50 PC3	CPEC 50 PC3 MM
1031		8-(azepan-4-yloxy)-6-ethynyl-N-(4-morpholinophenyl) quinazolin-2-amine	444, 2.05	++++		++++	
1032		(4-(5-chloro-6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)(morpholino)methanone	492.2, 2.26	++++		++++	
1033		(4-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)(morpholino)methanone	479.2, 3.4	++++		++++	
1034		4-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-isopropylbenzamide	451.1, 3.78	++++		++++	
1035		5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)-N-(4-morpholinophenyl) quinazolin-2-amine	451.2, 2.89	++++		++++	

PP028218.0002 (20366-156WO1)

1036		5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)-N-(3-morpholinophenyl) quinazolin-2-amine	451.2, 3.46	++++		++++	
1037		N-(3-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)acetamide	480.2, 2.5	++++		++++	
1038		4-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-cyclopropylbenzamide	449.2, 3.5	++++		++++	
1039		4-(6-ethynyl-7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)-N-isopropylbenzamide	476, 3.32	++++		++++	
1040		N-isopropyl-4-(7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)benzamide	452, 3.10	++++		+++	
1041		6-(6-ethynyl-2-(4-(morpholine-4-carbonyl)phenylamino)quinazolin-7-yl)-3,4-dihydroisoquinolin-1(2H)-one	504, 3.02	++++		+++	

PP028218.0002 (20366-156WO1)

1042		methyl 3-(7-(1-isopentyl-1H-pyrazol-4-yl)-8-methoxyquinazolin-2-ylamino)-5-(morpholinomethyl)phenylcarbamate		++++			++++
1043		N-(3-(7-(1-isobutyl-1H-pyrazol-4-yl)-8-methoxyquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide		++++			++++

PP028218.0002 (20366-156WO1)

The Compounds in Tables 1-4 were named using AutoNom 2000 (Automatic Nomenclature) for ISIS/Base or ChemDraw v. 10, implementing IUPAC standardized nomenclature. Superscripted characters are denoted by asterisks (*) before and after the character.

Further provided are compounds of Formula I and mixtures thereof where any asymmetric carbon atom(s) can have either the R or S configuration. Substituents at a double bond or a ring of the compounds of formula I may be present in either the cis (-Z-) or trans (-E-) configurations. The compounds may thus be present as mixtures of isomers, diastereomers, and enantiomers or may be present as pure isomers. In some embodiments, the compounds are enantiomerically pure where only one enantiomer is present. In other embodiments, the compound may be present as a mixture of enantiomers which includes more of one enantiomer than it does of the other.

Other embodiments provide methods for inhibiting PDK1 in a subject. More particularly, the present invention provides a method of inhibitng PDK1 comprising administering to a human or animal subject, a quinazoline compound as described herein. Such methods include administering a compound of Formula I, II or III to the subject.

The present invention further provides compositions including: a compound of Formula I, II or III and a pharmaceutically acceptable carrier or excipient.

Further methods of the invention are provided wherein compositions described herein are used for the treatment of cancer and reduction of tumor growth. In particular, the quinazoline compounds are useful in the treatment of human or animal (e.g., murine) cancers, including, for example, lung and bronchus; prostate; breast; pancreas; colon and rectum; thyroid; liver and intrahepatic bile duct; hepatocellular; gastric; glioma/glioblastoma; endometrial; melanoma; kidney and renal pelvis; urinary bladder; uterine corpus; uterine cervix; ovary; multiple myeloma; esophagus; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; melanoma; and villous colon adenoma. More particularly, the quinazoline compound of the invention is administered for the treatment of cancers of the prostate, lung, colon, or breast. In one such embodiment, the quinazoline compound is

administered to a subject in need thereof. In some such embodiments, the administration of the compound has an inhibiting effect upon tumor cell growth.

In accordance with another embodiment of the present invention, a therapeutic composition for inhibiting tumor cell growth in a subject is provided. Such compositions include an effective amount of a compound of the invention (i.e., a compound of Formula I, II or III) and at least one pharmaceutically acceptable carrier. In such embodiments, the composition is effective at inhibiting the growth of one or more mammalian tumor cells.

Pharmaceutical compositions that include the compounds described herein may include additives such as excipients. Suitable pharmaceutically acceptable excipients include processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more of these. Other suitable pharmaceutically acceptable excipients are described in **Remington: The Science And Practice Of Pharmacy,** Lippincott Williams & Wilkins; Baltimore, MD, 21st ed. (May 28, 2005), which is hereby incorporated herein by reference in its entirety and for all purposes as if fully set forth herein.

Pharmaceutical compositions that include the compounds of the invention may be in any form suitable for the intended method of administration, including, for example, as a solution, a suspension, or an emulsion. Liquid carriers are typically used in preparing solutions, suspensions, and emulsions. Liquid carriers contemplated for use in the practice of the present invention include, for example, water, saline, pharmaceutically acceptable organic solvent(s), pharmaceutically acceptable oils or fats, and the like, as well as mixtures of two or more of these. The liquid carrier may include other suitable pharmaceutically acceptable additives such as solubilizers, emulsifiers, nutrients, buffers, preservatives, suspending agents, thickening agents, viscosity regulators, stabilizers, and the like. Suitable organic solvents include, for example, monohydric alcohols, such as ethanol, and polyhydric alcohols, such as glycols. Suitable oils include, but are not limited to, soybean oil, coconut oil, olive oil, safflower oil, cottonseed oil, and the like. For parenteral administration, the carrier may be an oily ester such as ethyl oleate, isopropyl myristate, and the like. Compositions of the present invention may also be in the form

of microparticles, microcapsules, and the like, as well as combinations of any two or more of these.

The compounds and combinations of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form may include, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. Preferred lipids include phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods of forming liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq* (1976).

Controlled release delivery systems may also be used, such as a diffusion controlled matrix system or an erodible system, as described for example in: Lee, "Diffusion-Controlled Matrix Systems", pp. 155-198 and Ron and Langer, "Erodible Systems", pp. 199-224, in "Treatise on Controlled Drug Delivery", A. Kydonieus Ed., Marcel Dekker, Inc., New York 1992. The matrix may be, for example, a biodegradable material that can degrade spontaneously *in situ* and *in vivo* for, example, by hydrolysis or enzymatic cleavage, e.g., by proteases. The delivery system may be, for example, a naturally occurring or synthetic polymer or copolymer, for example in the form of a hydrogel. Exemplary polymers with cleavable linkages include polyesters, polyorthoesters, polyanhydrides, polysaccharides, poly(phosphoesters), polyamides, polyurethanes, poly(imidocarbonates) and poly(phosphazenes).

The compounds of the invention may be administered enterally, orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations that include conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. For example, suitable modes of administration include oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intramuscular, intraperitoneal, intranasal, subdermal, rectal, and the like. Topical administration may also include the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used

herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will, therefore, melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also include, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also include buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

Effective amounts of the compounds of the invention generally include any amount sufficient to detectably treat the disorders described herein.

PP028218.0002

Successful treatment of a subject in accordance with the invention may result in a reduction or alleviation of symptoms in a subject afflicted with a medical or biological disorder. For example, treatment may halt the further progression of the disorder, or may prevent or retard development of the disorder.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

DEFINITIONS

As used above and elsewhere herein the following terms and abbreviations have the meanings defined below:

AcH	Acetic Acid
ATP	Adenosine triphosphate
BCG	Mycobacterium bovis bacillus Calmette-Guerin
Bn	Benzyl
BSA	Bovine Serum Albumin
DCM	Dichloromethane
DIEA	N,N-diisopropyl-ethylamine
EDC	1-(3-Dimethylaminopropyl)3-ethylcarbodiimide hydrochloride
FHA	Filamentous haemaglutinin
GCMS	Gas Chromatography / Mass Spectroscopy
H. Pylori	Helicobacter Pylori
HBr	Hydrogen Bromide
HPLC	High Performance Liquid Chromatography

PP028218.0002

IC_{50} value	The concentration of an inhibitor that causes a 50 % reduction in a measured activity.
IFN	Interferon
IL	Interleukin
IMS	Immunomagnetic separation
IPV	Inactivated polio virus
LCMS	Liquid Chromatography / Mass Spectroscopy
LPS	Lipid polysaccharide
MAb or mAb	Monoclonal Antibody
MeOH	Methanol
MW	Molecular Weight
NMR	Nuclear magnetic resonance
OMV	Outer membrane vesicle
PBMC	Peripheral blood mononuclear cells
Rt	Room temperature (25°C)
tBOK	Potassium Tertiary Butoxide
TEA	Triethylamine
OTf	Triflate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography and/or Tender Loving Care
TMS	Trimethylsilyl
TNF-	Tumour necrosis factor-alpha

Reference to "quinazolines" (as pertaining to quinazolines of the present invention), indicates compounds having the general structure of Formula I, II or III as described herein. In some embodiments, the quinazolines include the compounds listed in Tables 1-5, *infra.*

"Modulating" refers to inducing or suppressing.

A "disease associated with cellular proliferation" includes, but is not limited to cancers, for example cancers of the prostate, lung, colon and breast, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis, proliferative diabetic

retinopathy (PDR), hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, angiogenesis, and endotoxic shock.

The term "effective amount" is an amount necessary or sufficient to realize a desired biological effect. For example, an effective amount of a compound to treat a disorder may be an amount necessary to cause reduction or alleviation of symptoms in a subject afflicted with a medical or biological disorder. For example, treatment may halt the further progression of the disorder, or may prevent or retard development of the disorder. The effective amount may vary, depending, for example, upon the condition treated, weight of the subject and severity of the disease. One of skill in the art can readily determine the effective amount empirically without undue experimentation.

As used herein "an effective amount for treatment" refers to an amount sufficient to palliate, ameliorate, stabilize, reverse, slow or delay progression of a condition such as a disease state.

A "subject" or "patient" is meant to describe a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, monkey, rat, mouse, and other mammals.

As used herein, the term "pharmaceutically acceptable ester" refers to esters, which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Representative examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The compounds of the present invention can be used in the form of salts as in "pharmaceutically acceptable salts" derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-napthalenesulfonate, oxalate, pamoate, pectinate, sulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate,

tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained. The terms used in the claims are defined below.

"Alkyl" refers to saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3-), ethyl (CH_3CH_2-), *n*-propyl ($CH_3CH_2CH_2$-), isopropyl ($(CH_3)_2CH$-), *n*-butyl ($CH_3CH_2CH_2CH_2$-), isobutyl ($(CH_3)_2CHCH_2$-), *sec*-butyl ($(CH_3)(CH_3CH_2)CH$-), *t*-butyl ($(CH_3)_3C$-), *n*-pentyl ($CH_3CH_2CH_2CH_2CH_2$-), and neopentyl ($(CH_3)_3CCH_2$-).

"Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Alkyl interrupted with -O-, -S-, -SO-, -SO2-, -NH-, carbonyl, carbonylamino, or aminocarbonyl" refers to a C2-10 alkyl group in which an -O-, -S-, -SO-, -SO2-, -NH-, carbonyl, carbonylamino, or aminocarbonyl is inserted between the carbon atoms of the alkyl group. For

example, an ethylene radical interrupted with -O- is -C-O-C-. An ethylene radical interrupted with carbonyl is -C-C(=O)-C-.

"Alkoxy" refers to the group –O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, *sec*-butoxy, and *n*-pentoxy.

"Substituted alkoxy" refers to the group –O-(substituted alkyl) wherein substituted alkyl is defined herein.

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group $CH_3C(O)$-.

"Acylamino" refers to the groups –NRC(O)alkyl, -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)cycloalkenyl, -NRC(O)substituted cycloalkenyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl, -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic wherein R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, cycloalkenyl-C(O)O-, substituted cycloalkenyl-C(O)O-, heteroaryl-C(O)O-, substituted

heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Amino" refers to the group $-NH_2$.

"Substituted amino" refers to the group –NR'R" where R' and R" are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cylcoalkyl, $-SO_2$-cycloalkenyl, $-SO_2$-substituted cylcoalkenyl,$-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, and $-SO_2$-substituted heterocyclic and wherein R′ and R″ are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R′ and R″ are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R′ is hydrogen and R″ is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R′ and R″ are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R′ or R″ is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R′ nor R″ are hydrogen.

"Aminocarbonyl" refers to the group $-C(O)NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,

substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonyl" refers to the group $-C(S)NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the group $-NRC(O)NR^{10}R^{11}$ where R is hydrogen or alkyl and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonylamino" refers to the group $-NRC(S)NR^{10}R^{11}$ where R is hydrogen or alkyl and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,

heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein..

"Aminocarbonyloxy" refers to the group –O–C(O)$NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyl" refers to the group –$SO_2NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyloxy" refers to the group –O-$SO_2NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

PP028218.0002

"Aminosulfonylamino" refers to the group $-NR-SO_2NR^{10}R^{11}$ where R is hydrogen or alkyl and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkyenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkyenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Amidino" refers to the group $-C(=NR^{12})R^{10}R^{11}$ where R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic (*e.g.*, 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

"Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl,

aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Aryloxy" refers to the group –O-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

"Substituted aryloxy" refers to the group –O-(substituted aryl) where substituted aryl is as defined herein.

"Arylthio" refers to the group –S-aryl, where aryl is as defined herein.

"Substituted arylthio" refers to the group –S-(substituted aryl), where substituted aryl is as defined herein.

"Alkenyl" refers to alkenyl groups having from 2 to 6 carbon atoms and preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of alkenyl unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl,

PP028218.0002

cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy substitution is not attached to a vinyl (unsaturated) carbon atom.

"Alkynyl" refers to alkynyl groups having from 2 to 6 carbon atoms and preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of alkynyl unsaturation.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy substitution is not attached to an acetylenic carbon atom.

"Carbonyl" refers to the divalent group –C(O)– which is equivalent to –C(=O)–.

"Carboxyl" or "carboxy" refers to –COOH or salts thereof.

"Carboxyl ester" or "carboxy ester" refers to the groups -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-alkenyl, -C(O)O-substituted alkenyl, -C(O)O-alkynyl,

-C(O)O-substituted alkynyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-cycloalkyl, -C(O)O-substituted cycloalkyl, -C(O)O-cycloalkenyl, -C(O)O-substituted cycloalkenyl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -C(O)O-heterocyclic, and -C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"(Carboxyl ester)amino" refers to the group -NR-C(O)O-alkyl, substituted -NR-C(O)O-alkyl, -NR-C(O)O-alkenyl, -NR-C(O)O-substituted alkenyl, -NR-C(O)O-alkynyl, -NR-C(O)O-substituted alkynyl, -NR-C(O)O-aryl, -NR-C(O)O-substituted aryl, -NR-C(O)O-cycloalkyl, -NR-C(O)O-substituted cycloalkyl, -NR-C(O)O-cycloalkenyl, -NR-C(O)O-substituted cycloalkenyl, -NR-C(O)O-heteroaryl, -NR-C(O)O-substituted heteroaryl, -NR-C(O)O-heterocyclic, and -NR-C(O)O-substituted heterocyclic wherein R is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"(Carboxyl ester)oxy" refers to the group -O-C(O)O-alkyl, substituted -O-C(O)O-alkyl, -O-C(O)O-alkenyl, -O-C(O)O-substituted alkenyl, -O-C(O)O-alkynyl, -O-C(O)O-substituted alkynyl, -O-C(O)O-aryl, -O-C(O)O-substituted aryl, -O-C(O)O-cycloalkyl, -O-C(O)O-substituted cycloalkyl, -O-C(O)O-cycloalkenyl, -O-C(O)O-substituted cycloalkenyl, -O-C(O)O-heteroaryl, -O-C(O)O-substituted heteroaryl, -O-C(O)O-heterocyclic, and -O-C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Cyano" refers to the group –CN.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. Examples of suitable

cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

"Cycloalkenyl" refers to non-aromatic cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings and having at least one >C=C< ring unsaturation and preferably from 1 to 2 sites of >C=C< ring unsaturation.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refers to a cycloalkyl or cycloalkenyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Cycloalkyloxy" refers to –O-cycloalkyl.

"Substituted cycloalkyloxy refers to –O-(substituted cycloalkyl).

"Cycloalkylthio" refers to –S-cycloalkyl.

"Substituted cycloalkylthio" refers to –S-(substituted cycloalkyl).

"Cycloalkenyloxy" refers to –O-cycloalkenyl.

"Substituted cycloalkenyloxy refers to –O-(substituted cycloalkenyl).

PP028218.0002

"Cycloalkenylthio" refers to –S-cycloalkenyl.

"Substituted cycloalkenylthio" refers to –S-(substituted cycloalkenyl).

"Guanidino" refers to the group –NHC(=NH)NH_2.

"Substituted guanidino" refers to $-NR^{13}C(=NR^{13})N(R^{13})_2$ where each R^{13} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and two R^{13} groups attached to a common guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that at least one R^{13} is not hydrogen, and wherein said substituents are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Hydroxy" or "hydroxyl" refers to the group –OH.

"Heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (*e.g.*, pyridinyl or furyl) or multiple condensed rings (*e.g.*, indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Preferred heteroaryls include pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

"Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

"Heteroaryloxy" refers to –O-heteroaryl.

"Substituted heteroaryloxy refers to the group –O-(substituted heteroaryl).

PP028218.0002

"Heteroarylthio" refers to the group –S-heteroaryl.

"Substituted heteroarylthio" refers to the group –S-(substituted heteroaryl).

"Heterocycle" or "heterocyclic" or "heterocycloalkyl" or "heterocyclyl" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, including fused bridged and spiro ring systems, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, sulfonyl moieties.

"Substituted heterocyclic" or "substituted heterocycloalkyl" or "substituted heterocyclyl" refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

"Heterocyclyloxy" refers to the group –O-heterocycyl.

"Substituted heterocyclyloxy refers to the group –O-(substituted heterocycyl).

"Heterocyclylthio" refers to the group –S-heterocycyl.

"Substituted heterocyclylthio" refers to the group –S-(substituted heterocycyl).

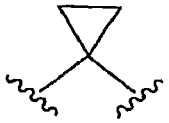
Examples of heterocycle and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, and tetrahydrofuranyl.

PP028218.0002

"Nitro" refers to the group $-NO_2$.

"Oxo" refers to the atom (=O) or ($-O^-$).

"Spirocycloalkyl" refers to divalent cyclic groups from 3 to 10 carbon atoms having a cycloalkyl ring with a spiro union (the union formed by a single atom which is the only common member of the rings) as exemplified by the following structure:



"Sulfonyl" refers to the divalent group $-S(O)_2-$.

"Substituted sulfonyl" refers to the group $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cylcoalkyl, $-SO_2$-cycloalkenyl, $-SO_2$-substituted cylcoalkenyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Substituted sulfonyl includes groups such as methyl-SO_2-, phenyl-SO_2-, and 4-methylphenyl-SO_2-.

"Sulfonyloxy" refers to the group $-OSO_2$-alkyl, $-OSO_2$-substituted alkyl, $-OSO_2$-alkenyl, $-OSO_2$-substituted alkenyl, $-OSO_2$-cycloalkyl, $-OSO_2$-substituted cylcoalkyl, $-OSO_2$-cycloalkenyl, $-OSO_2$-substituted cylcoalkenyl,$-OSO_2$-aryl, $-OSO_2$-substituted aryl, $-OSO_2$-heteroaryl, $-OSO_2$-substituted heteroaryl, $-OSO_2$-heterocyclic, $-OSO_2$-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thioacyl" refers to the groups H-C(S)-, alkyl-C(S)-, substituted alkyl-C(S)-, alkenyl-C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, cycloalkenyl-C(S)-, substituted

cycloalkenyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiol" refers to the group -SH.

"Thiocarbonyl" refers to the divalent group -C(S)- which is equivalent to –C(=S)-.

"Thione" refers to the atom (=S).

"Alkylthio" refers to the group -S-alkyl wherein alkyl is as defined herein.

"Substituted alkylthio" refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl (propyl and isopropyl), C_4 alkyl, C_5 alkyl, and C_6 alkyl.

"Stereoisomer" or "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers.

"Tautomer" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moeity such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyloxycabonyl" refers to the group (aryl)-(alkyl)-O-C(O)-.

PP028218.0002

The term "protected" or a "protecting group" with respect to hydroxyl groups, amine groups, and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art such as those set forth in Protective Groups in Organic Synthesis, Greene, T.W., John Wiley & Sons, New York, NY, (1st Edition, 1981) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane, triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methythiomethyl ether, benzyloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropyranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoracetate. Examples of protected amine groups include, but are not limited to, benzyl or dibenzyl, amides such as, formamide, acetamide, trifluoroacetamide, and benzamide; imides, such as phthalimide, and dithiosuccinimide; and others. In some embodiments, a protecting group for amines is a benzyl group. Examples of protected sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and S-4-picolyl thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

Quinazoline compounds of Formula I, II or III may exhibit the phenomenon of tautomerism, and the formula drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which possesses immunomodulatory activity and is not to be limited merely to any one tautomeric form utilized within the formula drawings.

Quinazolines of Formula I, II or III also may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. The invention encompasses both solvated and unsolvated forms which possess immunomodulatory activity.

The invention also includes isotopically-labeled quinazoline compounds, that are structurally identical to those disclosed above, except that one or more atom is/are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the

invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention, tautomers thereof, prodrugs thereof, and pharmaceutically acceptable salts of the compounds and of the prodrugs that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds of the invention are useful in pharmaceutical compositions for human or veterinary use where inhibition of PDK1 is indicated, for example, in the treatment of cellular proliferative diseases such as tumor and/or cancerous cell growth mediated by PDK1. In particular, the compounds are useful in the treatment of human or animal (e.g., murine) cancers, including, for example, lung and bronchus; prostate; breast; pancreas; colon and rectum; thyroid; liver and intrahepatic bile duct; hepatocellular; gastric; glioma/glioblastoma; endometrial; melanoma; kidney and renal pelvis; urinary bladder; uterine corpus; uterine cervix; ovary; multiple myeloma; esophagus; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; melanoma; and villous colon adenoma. In some preferred embodiments, the compounds of the invention are used to treat cancers of the prostate, lung, colon, and breast.

In other aspects, the invention provides methods for manufacture of PDK1 inhibitor compounds. It is further contemplated that, in addition to the compounds of Formulas I-III, intermediates, and their corresponding methods of syntheses are included within the scope of the embodiments.

PP028218.0002

In further embodiments, the present invention provides for compounds of Formula I, II, or III for inhibition of Cdk1 and/or Cdk2. Another embodiment provides a method of treating cancer responsive to inhibition of Cdk1, comprising administering a compound of Formula I, II, or III. Another embodiment provides a method of treating cancer responsive to inhibition of Cdk2, comprising administering a compound of Formula I, II, or III.

In further embodiment, the invention provides methods of inhibiting phosphorylation of Akt comprising administering a compound of Formula I, II, or III to a human in need thereof. Another embodiment provides a method of treating cancer responsive to inhibition of phosphorylation of Akt, comprising administering a compound of Formula I, II, or III. Another embodiment provides a method of inhibiting phosphorylation of Akt comprising contacting a cell with a compound of Formula I, II, or III.

In further embodiments, the invention provides methods of inhibiting PDK1 comprising orally administering a compound of Formula I, II, or III to a human in need thereof. In a more particular embodiment the human is suffering from cancer. In a more particular embodiment the cancer is responsive to treatment with a compound that inhibits phosphorylation of PDK1. In another embodiment the compound is orally bioavailable.

In some embodiments of the methods of inhibiting PDK1 using a PDK1 inhibitor compound described herein, the IC_{50} value of the compound is less than or equal to about 1 mM with respect to PDK1. In other such embodiments, the IC_{50} value is less than or equal to about 100 μM, is less than or equal to about 25 μM, is less than or equal to about 10 μM, is less than or equal to about 1 μM, is less than or equal to about 0.1 μM, is less than or equal to about 0.050 μM, or is less than or equal to about 0.010 μM.

In one embodiment, a method of reducing PDK1 activity in a human or animal subject is provided. In the method, a compound of the any of the aforementioned embodiments is administered in an amount effective to reduce PDK1 activity.

In some embodiments of the method of inhibiting PDK1 using a PDK1 inhibitor compound of the embodiments, the IC_{50} value of the compound is between about 1 nM to about 10 nM. In other such embodiments, the IC_{50} value is between about 10 nM to about 50 nM, between about 50 nM to about 100 nM, between about 100 nM to about 1 μM, between about 1 μM to about 25 μM, or is between about 25 μM to about 100 μM.

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Another embodiment provides methods of treating a PDK1-mediated disorder. In one method, an effective amount of a PDK1 inhibitor compound is administered to a patient (e.g., a human or animal subject) in need thereof to mediate (or modulate) PDK1 activity. In other such embodiments the PDK1-mediated disorder is cancer.

Still another embodiment provides methods of treating diseases characterized by "abnormal cellular proliferation." The term "abnormal cellular proliferation" includes, for example, any disease or disorder characterized by excessive or pathologically elevated cell growth such as is characteristic of various cancers and non-cancer proliferative disorders.

Example cancers include, for example, lung cancer, bronchial cancer, prostate cancer, breast cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, thyroid cancer, liver cancer, intrahepatic bile duct cancer, hepatocellular cancer, gastric cancer, glioma/glioblastoma, endometrial cancer, melanoma, kidney cancer, renal pelvic cancer, urinary bladder cancer; uterine corpus cancer; uterine cervical cancer, ovarian cancer, multiple myeloma, esophageal cancer, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, myeloid leukemia, brain cancer, oral cavity cancer, and pharyngeal cancer, laryngeal cancer, small intestinal cancer, non-Hodgkin lymphoma, and villous colon adenoma.

Example non-cancer proliferative disorders include neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis, proliferative diabetic retinopathy (PDR), hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, angiogenesis, and endotoxic shock.

In some embodiments, the invention provides pharmaceutical compositions including at least one compound of Formula I, II, or III, together with one or more pharmaceutically acceptable carriers suitable for administration to a human or animal subject, either alone or together with other agents, for example, anticancer agents.

In further embodiments, the invention provides methods of treating human or animal subjects suffering from a cellular proliferative disease, such as cancer. In some such embodiments, the invention provides methods of treating a human or animal subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, II, or III, either alone or in combination with other anticancer agents.

In particular, compositions will either be formulated together as a combination

therapeutic or administered separately. Anticancer agents for use with the preferred embodiments include, but are not limited to, one or more of the following set forth below:

A. Kinase Inhibitors

Kinase inhibitors for use as anticancer agents in conjunction with the compositions of the preferred embodiments include inhibitors of Epidermal Growth Factor Receptor (EGFR) kinases such as small molecule quinazolines, for example gefitinib (US 5457105, US 5616582, and US 5770599), ZD-6474 (WO 01/32651), erlotinib (Tarceva®, US 5,747,498 and WO 96/30347), and lapatinib (US 6,727,256 and WO 02/02552); Vascular Endothelial Growth Factor Receptor (VEGFR) kinase inhibitors, including SU-11248 (WO 01/60814), SU 5416 (US 5,883,113 and WO 99/61422), SU 6668 (US 5,883,113 and WO 99/61422), CHIR-258 (US 6,605,617 and US 6,774,237), vatalanib or PTK-787 (US 6,258,812), VEGF-Trap (WO 02/57423), B43-Genistein (WO-09606116), fenretinide (retinoic acid p-hydroxyphenylamine) (US 4,323,581), IM-862 (WO 02/62826), bevacizumab or Avastin® (WO 94/10202), KRN-951, 3-[5-(methylsulfonylpiperadine methyl)-indolyl]-quinolone, AG-13736 and AG-13925, pyrrolo[2,1-f][1,2,4]triazines, ZK-304709, Veglin®, VMDA-3601, EG-004, CEP-701 (US 5,621,100), Cand5 (WO 04/09769); Erb2 tyrosine kinase inhibitors such as pertuzumab (WO 01/00245), trastuzumab, and rituximab; Akt protein kinase inhibitors, such as RX-0201; Protein Kinase C (PKC) inhibitors, such as LY-317615 (WO 95/17182), and perifosine (US 2003171303); Raf/Map/MEK/Ras kinase inhibitors including sorafenib (BAY 43-9006), ARQ-350RP, LErafAON, BMS-354825 AMG-548, and others disclosed in WO 03/82272; Fibroblast Growth Factor Receptor (FGFR) kinase inhibitors; Cell Dependent Kinase (CDK) inhibitors, including CYC-202 or roscovitine (WO 97/20842 and WO 99/02162); Platelet-Derived Growth Factor Receptor (PDGFR) kinase inhibitors such as CHIR-258, 3G3 mAb, AG-13736, SU-11248 and SU6668; and Bcr-Abl kinase inhibitors and fusion proteins such as STI-571 or Gleevec® (imatinib).

B. Anti-Estrogens

Estrogen-targeting agents for use in anticancer therapy in conjunction with the compositions of the preferred embodiments include Selective Estrogen Receptor Modulators (SERMs) including tamoxifen, toremifene, raloxifene; aromatase inhibitors including Arimidex® or anastrozole; Estrogen Receptor Downregulators (ERDs) including Faslodex® or fulvestrant.

PP028218.0002

C. Anti-Androgens

Androgen-targeting agents for use in anticancer therapy in conjunction with the compositions of the preferred embodiments include flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids.

D. Other Inhibitors

Other inhibitors for use as anticancer agents in conjunction with the compositions of the preferred embodiments include protein farnesyl transferase inhibitors including tipifarnib or R-115777 (US 2003134846 and WO 97/21701), BMS-214662, AZD-3409, and FTI-277; topoisomerase inhibitors including merbarone and diflomotecan (BN-80915); mitotic kinesin spindle protein (KSP) inhibitors including SB-743921 and MKI-833; proteasome modulators such as bortezomib or Velcade® (US 5,780,454), XL-784; and cyclooxygenase 2 (COX-2) inhibitors including non-steroidal antiinflammatory drugs I (NSAIDs).

E. Cancer Chemotherapeutic Drugs

Particular cancer chemotherapeutic agents for use as anticancer agents in conjunction with the compositions of the preferred embodiments include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®, US 2004073044), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, gemcitabine (Gemzar® or difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-

thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

F. Alkylating Agents

Alkylating agents for use in conjunction with the compositions of the preferred embodiments for anticancer therapeutics include VNP-40101M or cloretizine, oxaliplatin (US 4,169,846, WO 03/24978 and WO 03/04505), glufosfamide, mafosfamide, etopophos (US 5,041,424), prednimustine; treosulfan; busulfan, irofluven (acylfulvene), penclomedine, pyrazoloacridine (PD-115934); O6-benzylguanine, decitabine (5-aza-2-deoxycytidine), brostallicin, mitomycin C (MitoExtra), TLK-286 (Telcyta®), temozolomide, trabectedin (US 5,478,932), AP-5280 (Platinate formulation of Cisplatin), porfiromycin, and clearazide (meclorethamine).

G. Chelating Agents

Chelating agents for use in conjunction with the compositions of the preferred embodiments for anticancer therapeutics include tetrathiomolybdate (WO 01/60814); RP-697, Chimeric T84.66 (cT84.66), gadofosveset (Vasovist®), deferoxamine, and bleomycin optionally in combination with electorporation (EPT).

H. Biological Response Modifiers

Biological response modifiers, such as immune modulators, for use in conjunction with the compositions of the preferred embodiments for anticancer therapeutics include staurosprine and macrocyclic analogs thereof, including UCN-01, CEP-701 and midostaurin (see WO 02/30941, WO 97/07081, WO 89/07105, US 5,621,100, WO 93/07153, WO 01/04125, WO 02/30941, WO 93/08809, WO 94/06799, WO 00/27422, WO 96/13506 and WO 88/07045); squalamine (WO 01/79255); DA-9601 (WO 98/04541 and US 6,025,387); alemtuzumab; interferons (e.g. IFN-a, IFN-b etc.); interleukins, specifically IL-2 or aldesleukin as well as IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, and active biological variants thereof having amino acid sequences greater than 70% of the native human sequence; altretamine (Hexalen®); SU 101 or leflunomide (WO 04/06834 and US 6,331,555); imidazoquinolines such as resiquimod and imiquimod (US 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 6,083,505, 5,352,784, 5,494,916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, and 5,525,612) or 2,4-diaminoimidazoquinolines (WO 06/31878); and SMIPs,

including benzazoles, anthraquinones, thiosemicarbazones, and tryptanthrins (WO 04/87153, WO 04/64759, and WO 04/60308).

I. Cancer Vaccines:

Anticancer vaccines for use in conjunction with the compositions of the preferred embodiments include Avicine® (*Tetrahedron Lett.* 26:2269-70 (1974)); oregovomab (OvaRex®); Theratope® (STn-KLH); Melanoma Vaccines; GI-4000 series (GI-4014, GI-4015, and GI-4016), which are directed to five mutations in the Ras protein; GlioVax-1; MelaVax; Advexin® or INGN-201 (WO 95/12660); Sig/E7/LAMP-1, encoding HPV-16 E7; MAGE-3 Vaccine or M3TK (WO 94/05304); HER-2VAX; ACTIVE, which stimulates T-cells specific for tumors; GM-CSF cancer vaccine; and Listeria monocytogenes-based vaccines.

J. Antisense Therapy:

Anticancer agents for use in conjunction with the compositions of the preferred embodiments also include antisense compositions, such as AEG-35156 (GEM-640); AP-12009 and AP-11014 (TGF-beta2-specific antisense oligonucleotides); AVI-4126; AVI-4557; AVI-4472; oblimersen (Genasense®); JFS2; aprinocarsen (WO 97/29780); GTI-2040 (R2 ribonucleotide reductase mRNA antisense oligo) (WO 98/05769); GTI-2501 (WO 98/05769); liposome-encapsulated c-Raf antisense oligodeoxynucleotides (LErafAON) (WO 98/43095); and Sima-027 (RNAi-based therapeutic targeting VEGFR-1 mRNA).

The foregoing may be better understood by reference to the following Examples that are presented for illustration and not to limit the scope of the inventive concepts. The Example compounds and their analogs are easily synthesized by one skilled in the art from procedures described herein, as well as in patents or patent applications listed herein which are all hereby incorporated by reference in their entireties and for all purposes as if fully set forth herein.

EXAMPLES

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2695 Separation Module (Milford, MA). The analytical columns were reversed phase Phenomenex Luna C18 -5 μ, 4.6 x 50 mm, from Alltech (Deerfield, IL). A gradient elution was

used (flow 2.5 mL/min), typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 10 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA).

In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

Mass spectrometric analysis was performed on one of two LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 4 min period ; flow rate 0.8 mL/min; molecular weight range 200-1500; cone Voltage 20 V; column temperature 40°C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% acetonitrile in water with 0.05% TFA over a 4 min period ; flow rate 0.8 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses were reported as those of the protonated parent ions.

GCMS analysis is performed on a Hewlett Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; injector volume: 1 μL; initial column temperature: 50°C; final column temperature: 250°C; ramp time: 20 minutes; gas flow rate: 1 mL/min; column: 5% phenyl methyl siloxane, Model No. HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 300 MHz NMR (Palo Alto, CA). The spectral reference was either TMS or the known chemical shift of the solvent. Some compound samples were run at elevated temperatures (e.g., 75°C) to promote increased sample solubility.

The purity of some of the compounds is assessed by elemental analysis (Desert Analytics, Tucson, AZ).

Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

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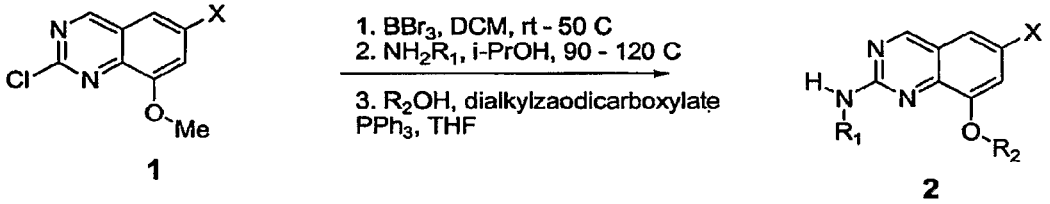
Preparative separations are carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a Waters 2767 Sample Manager, C-18 reversed phase column, 30X50 mm, flow 75 mL/min. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography are dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous ammonia (or ammonium hydroxide), and triethyl amine. Typical solvents employed for the reverse phase HPLC are varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

Example 1

Preparation of 3-(8-(1-Methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide



1 **2**

1a: X = H, 1b: X = Br

Step1. Preparation of 2-Chloroquinazolin-8-ol

To a 0.55M solution of 2-chloro-8-methoxyquinazoline in DCM was added boron tribromide (2.2 eq. of a 1.0 M solution in DCM) over 5 minutes at 0 °C. The reaction mixture was stirred at ambient temperature for 22 hours, and then cooled to –5 °C for 30 minutes. The precipitate was collected by vacuum filtration and then stirred in ice water for 30 minutes. The solid was collected by vacuum filtration and rinsed with 2-propanol. The off-white solid was dried in a desiccator to give the desired product in 79% yield. ES/MS *m/z* 181 (MH^+).

Step 2. Preparation of 3-(8-Hydroxyquinazolin-2-ylamino)benzenesulfonamide

To a 0.3 M solution of 2-chloroquinazolin-8-ol in 2-propanol was added sulfanilamide (1.0 eq). The reaction was stirred at 90 °C for 14 hours. The hydrochloride was collected by vacuum filtration and then stirred in aqueous sodium bicarbonate. The solid was collected by vacuum filtration and rinsed with water. The off-white solid was dried in a desiccator to give the desired product in 93% yield. ES/MS *m/z* 317 (MH^+).

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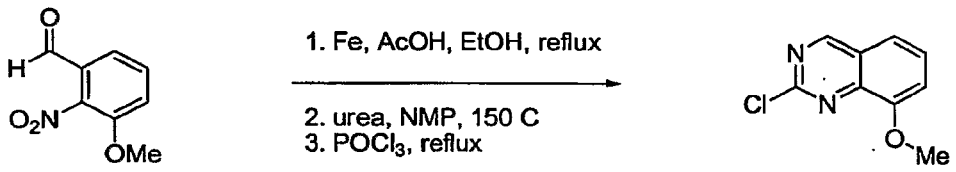
Step 3. Preparation of 3-(8-(1-Methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide

To a 0.3M solution of triphenylphosphine (1.5 eq) in THF was added di-tert-butylazodicarboxylate (1.5 eq). The mixture was stirred 15 minutes at ambient temperature. 4-Hydroxy-1-methylpiperidine (4.5 eq) was added. The mixture was stirred 15 minutes at ambient temperature. 3-(8-Hydroxyquinazolin-2-ylamino)benzenesulfonamide (1.0 eq) was added. The mixture was stirred an additional 1 hour. The crude mixture was concentrated, purified by RPHPLC, and lyophilized to give the desired product in 24.2% yield. ES/MS *m/z* 414 (MH^+).

Example 2

Step 1. Preparation of 2-chloro-8-methoxyquinazoline



3 1a

Step 1. Preparation of 2-amino-3-methoxybenzaldehyde

Iron powder (40 g) was slowly added to a stirred solution of 3-methoxy-2-nitrobenzaldehyde (**1**) (70 g, 386 mmole) in AcOH gal. (100 mL) and EtOH abs. (400 mL). The reaction was cooled using an ice bath followed by addition of con. HCL (1 mL). The reaction became exothermic. After stabilization of the reaction temperature, the reaction was heated to reflux. The reaction reached completion after ca. 20 minutes according to LCMS. The reaction mixture was cooled to RT and filtered. The filtrate was evaporated to a thick brown syrup. The dark residue was dissolved in EtOAc (500 mL) and water (200 mL). The mixture was basified with NaOH 6M to ca. pH 10. The mixture was filtered over celite and the layers separated. The organic layer was washed with $NaHCO_3$ (2 x 100 mL), water (2 x 100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated to a dark amber oil. The oil was dried *in vacuo* to give 95% pure product 2-amino-3-methoxybenzaldehyde in 64% yield (37.2 g, 246 mmole).

PP028218.0002

Step 2. Preparation of 8-methoxyquinazolin-2-ol

Solid 2-amino-3-methoxybenzaldehyde (37.2 g, 0.246 mole), urea (158 g, 2.5 mole) and catalytic NH_4OAc (1 g) were thoroughly mixed together in a roundbottom flask. The solid mixture was heated in a 160 °C bath. The solids quickly melted and stirring was commenced. After about 15 minutes, solids start to precipitate from the hot solution. After adding NMP (150 mL) to dissolve the solids, the reaction was heated with stirring for an additional 30-45 minutes until complete as judged by LCMS. The hot reaction mixture was poured into vigorously stirred water (400 mL). The reaction flask was washed out with water (3 x 100 mL) and EtOAc (4 x 50 mL). After stirring ca. 30 minutes, mixture was filtered to collect the light solid precipitate. The solid filter cake was washed with portions of water and EtOAc to give a white solid. The solid was dried on the frit and *in vacuo* to give the product in 99% purity and 95% yield (41 g, 233 mmole).

Step 3. Preparation of 2-chloro-8-methoxyquinazoline

Neat $POCl_3$ (400 mL) was added to 8-methoxyquinazolin-2-ol (5.0 g, 28.4 mmole) with stirring and cooling over an ice bath under argon. After ca. 1 minute, the reaction was removed from the ice bath and stirred at RT for ca. 20 minutes until a fine yellow suspension was formed. The reaction, fitted with a reflux condenser, was heated in an oil bath at 140-145 °C. After about 1 hour, the reaction turned clear and colorless. LCMS showed that the reaction was complete. The $POCl_3$ was evaporated under reduced pressure, and dried *in vacuo*. After 12 hours, the residue was partitioned between EtOAc (300 mL) and sat. $NaHCO_3$ (200 mL). The mixture was stirred cautiously watching gas evolution until the pH reached ~8. The layers were separated and the organic layer was washed with $NaHCO_3$ (2 x 100 mL), water with 5% brine (2 x 100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated to a yellow solid. The crude product was purified by flash chromatography eluting with 50% EtOAc/Hexane and finishing with 100% EtOAc to produce a white solid after evaporating the correct fractions. The pure 2-chloro-8-methoxyquinazoline was isolated in 89% yield (4.9 g, 25.3 mmole).

Example 3

Step 1. Preparation of 6-bromo-2-chloro-8-methoxyquinazoline

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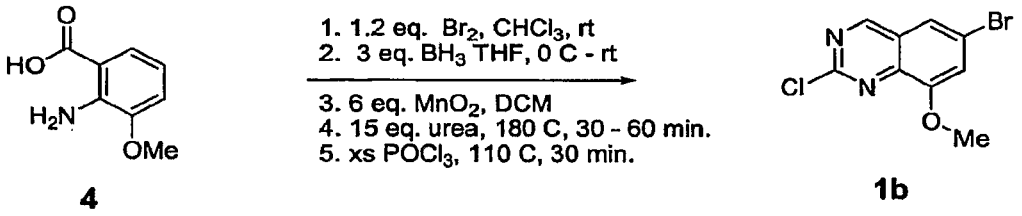

4 1b

Step 1. Preparation of 2-amino-5-bromo-3-methoxybenzoic acid

To a 0.24 M chloroform solution of 2-amino-3-methoxybenzoic acid (4, 11.87 g, 71.7 mmol) at 0 °C was added bromine (1.08 eq. 0.31 M) in chloroform dropwise. The mixture was warmed to room temperature and stirred under argon for 16 hours. The resulting precipitate was collected by filtration and washed thoroughly with chloroform. The crude material was dried in vacuo to give the title as an HBr salt in 99% yield. ES/MS *m/z* 248/250 (MH^+).

Step 2. Preparation of (2-amino-5-bromo-3-methoxyphenyl)methanol

To a 0.24 M THF suspension 2-amino-5-bromo-3-methoxybenzoic acid (71.7 mmol) at 0 °C was added borane THF solution (1 M, 220 mL, 220 mmol). The mixture was stirred under argon at room temperature for 66 hours. The reaction was quenched by adding ethanol (15 mL) at 0 °C and stirred for 15 minutes. The mixture was poured into water and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated *in vacuo* to give crude material as a white solid (10.16 g, 62% yield). ES/MS *m/z* 230/232 (MH^+).

Step 3. Preparation of 2-amino-5-bromo-3-methoxybenzaldehyde

To a 0.15 M chloroform solution of (2-amino-5-bromo-3-methoxyphenyl)methanol (10.16 g, 43.96 mmol) was added manganese dioxide (19.9 g, 280.5 mmol). The mixture was stirred under argon at room temperature for 16 hours. The resulting mixture was filtered through celite and washed with dichloromethane. The filtrate was concentrated to dryness and used in next step. ES/MS *m/z* 228/230 (MH^+).

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Step 4. Preparation of 6-bromo-8-methoxyquinazolin-2-ol

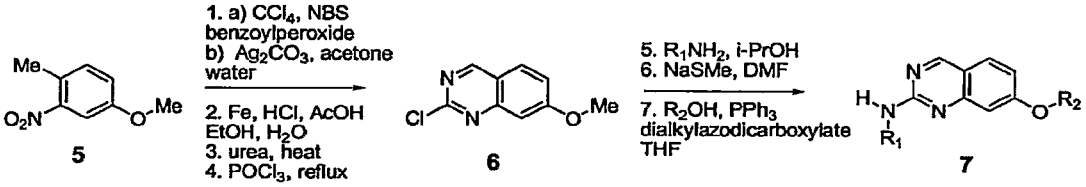
The mixture of 2-amino-5-bromo-3-methoxybenzaldehyde (43.96 mmol, crude material from step 3) and urea (35 g, 583 mmol) from the previous step was heated to 180 °C under argon for 1 hour. Water (300 mL) was added after cooling to room temperature. The solid was collected by filtration and air dried to give 12.45 g of powder. ES/MS *m/z* 254/256 (MH^+).

Step 5. Preparation of 6-bromo-2-chloro-8-methoxyquinazoline

A suspension of 6-bromo-8-methoxyquinazolin-2-ol (43.96 mmol) in $POCl_3$ (120 mL) was heated to 110 °C for 30 minutes The mixture was cooled to room temperature, evaporated $POCl_3$ and partitioned between water and dichloromethane. The organic portion was concentrated to give a crude material which was purified by column chromatography (silica gel, eluted with 2% MeOH in dichloromethane) to yield pure material as a yellow solid in 30% yield (3 steps, 3.62 g). ES/MS *m/z* 272/274 (MH^+).

Example 4

Preparation of 3-(7-(1-Methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide



Step 1. Preparation of 4-methoxy-2-nitrobenzaldehyde

Compound **5** (20.43 g, 0.122 mol, 1.0 eq) was dissolved in 480 ml of CCl_4 under Ar. NBS (48.94 g, 0.275 mol, 2.2 eq) was added to the solution as a solid in one portion followed by addition of benzoyl peroxide (0.67 g, 2.76 mmol). The reaction mixture was stirred under reflux conditions for 4.5 hours. The ^1H NMR of an aliquot showed ~ 90% conversion of starting material to dibromo derivative.

The reaction mixture was cooled to RT, and concentrated. CCl_4 was chased twice with acetone. The residue was taken into acetone (1L) and Ag_2CO_3 (37.1 g, 0.135 mol, 1.1 eq) was added followed by addition of water (100 mL). The reaction mixture was left stirring at RT overnight. TLC (EtOAc: Hexanes= 3:7) showed a new spot. The reaction mixture was filtered though

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celite, and the filter cake was washed with acetone and the filtrate was concentrated. 340 mL of H_2O was added to the crude and the product was extracted with EtOAc (800 mL, 400 mL). The emulsion that formed was filtered through celite and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give 8.27 g of crude material, which was purified by column chromatography (EtOAc/Hexanes) giving 14.7 g (67% yield) of pure compound.

Step 2. Preparation of 2-Formyl-5-methoxyaniline

A flask was charged with 4-methoxy-2-nitrobenzaldehyde (14.7 g, 81.2 mmol, 1.0eq), EtOH (270 mL), glacial AcOH (270 mL), H_2O (135 mL), degassed and filled with argon. Then Fe powder (325 mesh) (27.2 g, 0.49 mol, 6.0 eq) was added followed by addition of concentrated HCl (12.24 mL, 0.148 mol, 1.8 eq). After stirring the reaction mixture for 1 hour at 60-65°C (oil bath) TLC (EtOAc/Hex = 4:6) showed that no starting material was left. The reaction mixture was cooled down to RT, diluted with 200 mL of H_2O and neutralized with Na_2CO_3 to pH= 7-8. The product was extracted into CH_2Cl_2. The emulsion that formed was filtered through celite, organic layer was washed with brine, dried over Na_2SO_4, concentrated giving 12.0 g (98% yield) of the title compound.

Step 3. Preparation of 2-Hydroxy-7-methoxyquinazoline

2-Formyl-5-methoxyaniline (11.93 g, 79.5 mmol, 1.0eq) and urea (38.0g, 0.636 mol, 8.0 eq) were mixed, ground into a fine powder and placed into a 1L 2-neck flask equipped with a mechanical stirrer and an air condenser. The flask was placed into a preheated (160°C) oil bath. The reaction mixture melted and was stirred at 170-180°C for 1 hour until it solidified forming yellowish-brown solid. The reaction mixture was cooled to RT, crushed, mixed with 70 mL of H_2O and stirred for ~1 hour at RT. The solid was filtered, washed with 150 mL of H_2O and 20 mL of ice cold Et_2O. The yellow solid thus obtained was dried over P_4O_{10} under high vacuum for several hours and the crude material (12.57 g) was used for the next step without purification.

Step 4. Preparation of 2-Chloro-7-methoxyquinazoline

The crude 2-Hydroxy-7-methoxyquinazoline (12.48 g) was mixed with 170 mL of $POCl_3$, and the reaction mixture was stirred under reflux conditions for 6 hours. $POCl_3$ was removed using a

rotovap. The crude was mixed with ~500 mL of $CHCl_3$, stirred for 1 hour at RT, neutralized with Na_2CO_3 (pH 6-7) and the product was then extracted into chloroform. The emulsion that formed was filtered through celite, organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (EtOAc/Hex) followed by recrystallization from EtOAc/Hex giving 4.4g of pure compound **6** (the combined yield for two last steps is 29%).

Step 5. Preparation of 3-(7-Methoxyquinazolin-2-ylamino)benzenesulfonamide
To a 0.3 M solution of 2-chloro-7-methoxyquinazoline **6** in 2-propanol was added sulfanilamide (1.0 eq). The reaction was stirred at 90 °C for 20 hours. The hydrochloride was collected by vacuum filtration and then stirred in aqueous sodium bicarbonate. The solid was collected by vacuum filtration and rinsed with water. The off-white solid was dried in vacuum to give the desired product in 95% yield. ES/MS *m/z* 331 (MH^+).

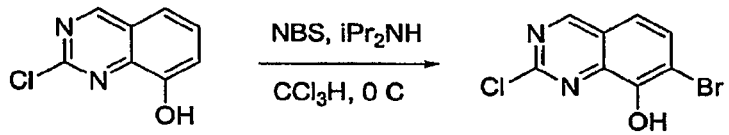
Step 6. Preparation of 3-(7-Hydroxyquinazolin-2-ylamino)benzenesulfonamide
To a 0.02M solution of 3-(7-Methoxyquinazolin-2-ylamino)benzenesulfonamide in NMP was added sodium thiomethoxide (5.0 eq) at ambient temperature. The reaction was stirred at 80 °C for 3 hours. The solid was collected by vacuum filtration and was partitioned between ethyl acetate and water. Saturated ammonium hydrochloride was added to aqueous phase until the PH = 6. Aqueous phase was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated to give desired product in 85% yield. ES/MS *m/z* 317 (MH^+).

Step 7. 3-(7-(1-Methylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide
To a 0.2M solution of triphenylphosphine (1.5 eq) in THF was added di-tert-butylazodicarboxylate (1.5 eq). The mixture was stirred 15 minutes at ambient temperature. 4-Hydroxy-1-methylpiperidine (4.0 eq) was added, and the mixture was stirred 15 minutes at ambient temperature. 3-(7-Hydroxyquinazolin-2-ylamino)benzenesulfonamide (1.0 eq) was then added, and the mixture was stirred an additional 10 hours. The crude mixture was concentrated, purified by RPHPLC, and lyophilized to give the desired product 7 in 18% yield. ES/MS *m/z* 414 (MH^+).

PP028218.0002

Example 5

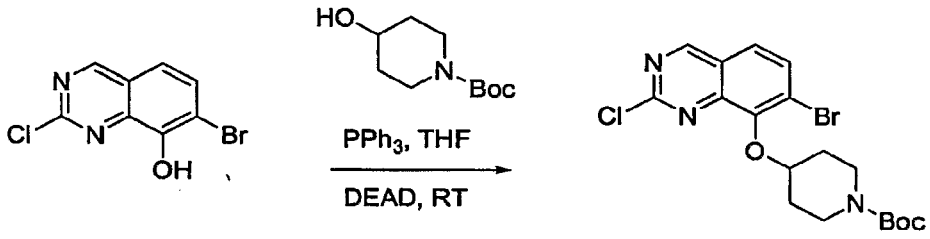
Preparation of 7-bromo-2-chloroquinazolin-8-ol



Solid NBS (1.09 g, 6.11 mmole) was added to a stirred solution of 2-chloroquinazolin-8-ol (1.10 g, 6.11 mmole) and diisopropyl amine (2.2 mL, 15.30 mmole) in $CHCl_3$ (60 mL) at -5 °C under argon. After stirring at -5 to 0 °C for 1 hour, LCMS showed that the reaction was complete. The reaction was evaporated to a residue which was dissolved in DMSO (5 mL) and purified by prep. HPLC. The pure product was obtained as a white solid in 51% yield (800 mg, 3.08 mmole).

Example 6

Preparation of *tert*-butyl 4-(7-bromo-2-chloroquinazolin-8-yloxy)piperidine-1-carboxylate

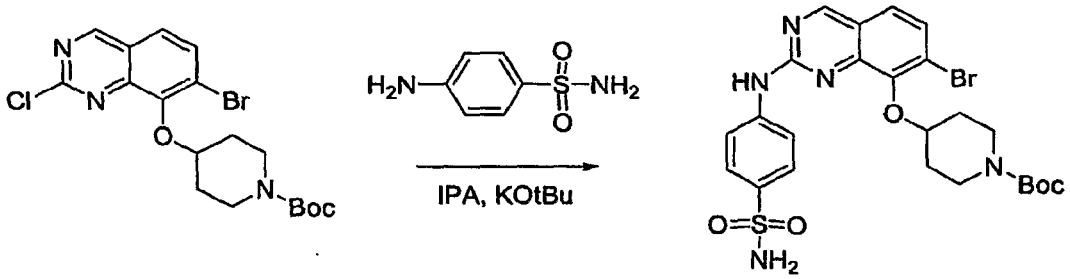


A solution of DEAD (404 mg, 2.32 mmole) in THF (0.5 mL) was added to a solution of 7-bromo-2-chloroquinazolin-8-ol (400 mg, 1.54 mmole), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (621 mg, 3.09 mmole) and PPh_3 (610 mg, 2.32 mmole) in THF (5.5 mL) at RT. After 1.5 hours, silica gel was added to the reaction which was evaporated to dryness and loaded onto a flash column. The product was eluted with 25% EtOAc/hexane to give *tert*-butyl 4-(7-bromo-2-chloroquinazolin-8-yloxy)piperidine-1-carboxylate in 80 % yield (545 mg, 1.23 mmole).

Example 7

Preparation of *tert*-butyl 4-(7-bromo-2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)piperidine-1-carboxylate

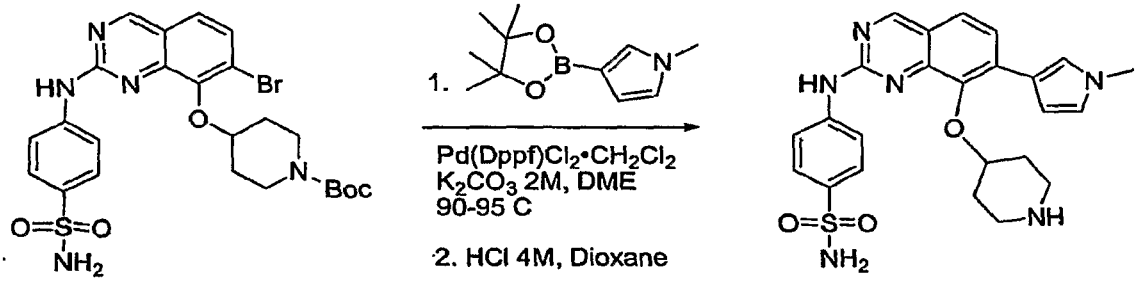
PP028218.0002



Solid KOtBu (442 mg, 3.95 mmole) was added to a solution of *tert*-butyl 4-(7-bromo-2-chloroquinazolin-8-yloxy)piperidine-1-carboxylate (500 mg, 1.13 mmole) and 4-aminobenzenesulfonamide (777 mg, 4.62 mmole) in IPA (15 mL). The reaction was sealed and heated to 105 °C with stirring. After 2.5 hours, AcOH was added to the reaction to pH 4 and the reaction was evaporated to a solid. The crude product was dissolved in DMSO (15 mL) and purified by prep. HPLC to give 241 mg of product in 37 % yield (417 mmole).

Example 8

Preparation of 4-(7-(1-methyl-1H-pyrrol-3-yl)-8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide



A 2M solution of K_2CO_3 (180 µL) was added to a mixture of *tert*-butyl 4-(7-bromo-2-(4-sulfamoylphenylamino)quinazolin-8-yloxy)piperidine-1-carboxylate (18 mg, 0.031 mmole), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (20 mg, 0.093 mmole) and palladium (4 mg, 0.005 mmole) in DME (0.6 mL). The reaction was sparged with argon, sealed and heated at 90-95 °C with stirring. After 90 minutes, LCMS showed that the reaction had reached completion. The Boc group was removed by adding 4M HCl (1.5 mL) in dioxane to the

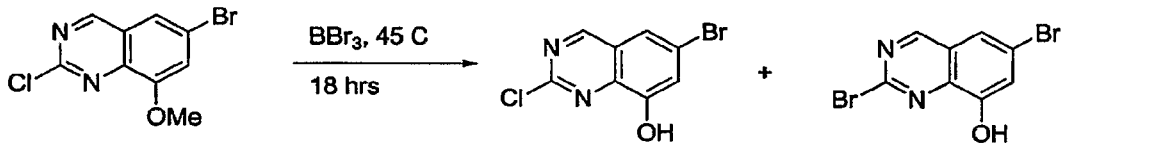
PP028218.0002

cooled reaction mixture. After 2 hours, the reaction was complete by LCMS. The reaction was filtered, evaporated, dissolved in DMSO (1 mL) and purified by prep. HPLC to give 3.4 mg of the pure product as a TFA salt.

Example 9

Synthesis of 4-(6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide (Compound 1015)

Step 1. Preparation of 6-bromo-2-chloroquinazolin-8-ol and 2,6-dibromoquinazolin-8-ol



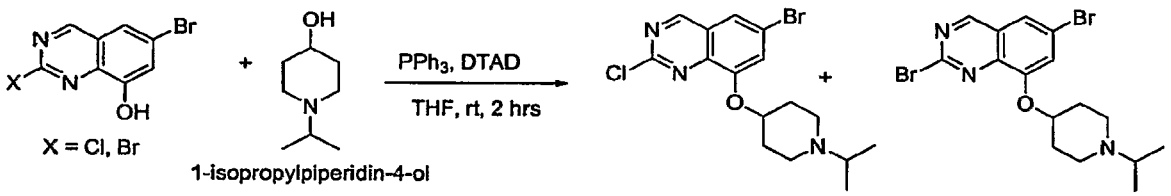
compound **1b** from Scheme 3 in Example 3

6-bromo-2-chloroquinazolin-8-ol

2,6-dibromoquinazolin-8-ol

To compound **1b** (1.26 g, 4.6 mmol) suspended in dichloromethane (20 mL) at 0 °C was added dropwise a dichloromethane solution of borontribromide (1 M, 28 mL, 28 mmol). The mixture was heated to 45 °C for 18 hrs. The resulting suspension was cooled and concentrated to dryness. The residue was cooled in ice bath and saturated $NaHCO_3$ aq. was added. The solid was collected and air dried to give desired product mixture. Without further purification, this was used in the next step.

Step 2. Preparation of 6-bromo-2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline and 2,6-dibromo-8-(1-isopropylpiperidin-4-yloxy)quinazoline



X = Cl, Br

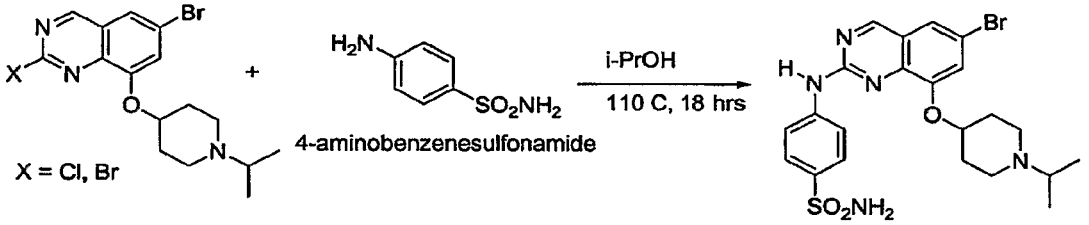
1-isopropylpiperidin-4-ol

Triphenylphosphine (0.49 g, 1.86 mmol), di-t-butylazodicarboxylate (0.42 g, 1.86 mmol) and 1-isoprpopylpiperidin-4-ol (0.54 g, 3.74 mmol) were mixed in anhydrous THF (6 mL) and stirred

PP028218.0002

at room temperature for 1.5 hrs. To this mixture was added the THF (5 mL) suspension of a mixture of 6-bromo-2-chloroquinazolin-8-ol and 2,6-dibromoquinazolin-8-ol (0.35 g). The reaction was stirred at room temperature for 2 hrs, worked up by pouring into water and extracted with EtOAc. The organic extracts were washed with brine, dried with sodium sulfate and concentrated in vacuo. The resulting residue was purified by column chromagraphy (silica gel, eluted with EtOAc/Hexanes 1:1 and DCM/MeOH 9:1) to give 0.25 g brown foam as desired product mixture. ES/MS *m/z* 384/386 (1:1) (MH^+ for 6-bromo-2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline) and 428/430/432 (1:2:1) (MH^+ for 2,6-dibromo-8-(1-isopropylpiperidin-4-yloxy)quinazoline).

Step 3. Preparation of 4-(6-bromo-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide



To the mixture of 6-bromo-2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline and 2,6-dibromo-8-(1-isopropylpiperidin-4-yloxy)quinazoline (0.15 g) in 1.5 mL of isopropanol was added 4-aminobenzenesulfonamide (81 mg, 0.47 mmol) and HCl in dioxane (4M, 100 μL). The mixture was heated to 100 °C for 15 hrs. Additional amount of 4-aminobenzenesulfonamide (0.2 g) was added and heating was continued at 120 °C for 18 hrs. The reaction was cooled to room temperature, diluted with $NaHCO_3$ (saturated aqueous) and extracted with EtOAc. The organic extracts were dried and concentrated to give a yellow foam containing desired product 4-(6-bromo-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 520/522 (MH^+).

Step 4. Preparation of 4-(6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide

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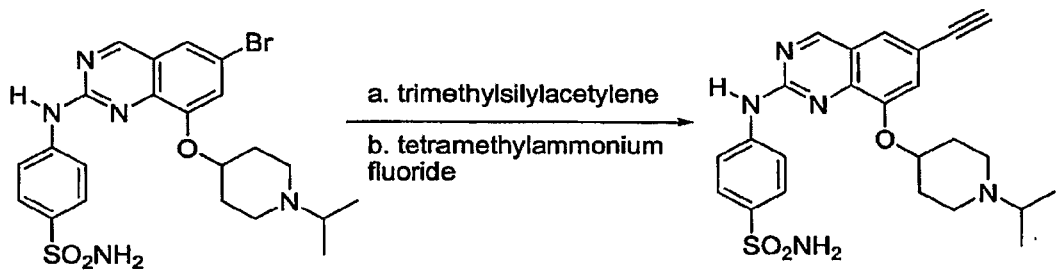
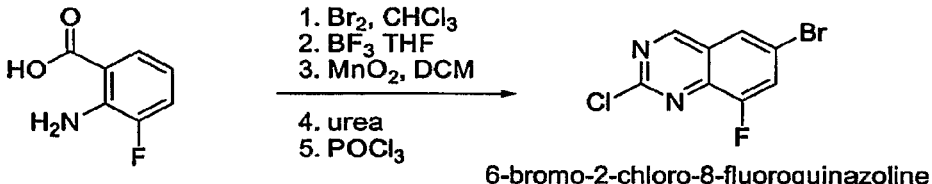


A mixture of 4-(6-bromo-8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide (crude, ~50% purity), trimethylsilylacetylene (0.2 mL), CuI (16 mg), $PdCl_2(dppf)_2$ (32 mg), triethylamine (0.8 mL) and dimethylforamide (0.8 mL) was microwaved at 120 °C for 10 min. The resulting dark brown mixture was diluted with THF (0.8 mL). Tetramethylammonium fluoride (30 mg) was added and the mixture was stirred at room temperature for 18 hrs. The resulting mixture was diluted with water and extracted with EtOAc. The organic extracts were dried with sodium sulfate and concentrated to give a residue which was purified by reverse phase HPLC. The pure fraction was collected and lyophilized to yield desired product as a TFA salt. ES/MS *m/z* 466 (MH^+).

Example 10

Synthesis of 6-bromo-2-chloro-8-fluoroquinazoline



2-amino-3-fluorobenzoic acid

6-bromo-2-chloro-8-fluoroquinazoline

Step 1. To a suspension of 2-amino-3-fluorobenzoic acid (5 g, 32.2 mmol) in chloroform (200 mL) was added dropwise bromine (1.1 equiv.) in chloroform (125 mL) solution. The mixture was stirred at room temperature for 16 hrs. The resulting white solid was collected by filtration and washed thoroughly with methylene chloride until the filtrate was colorless. The solid was air-dried to give 9.6 g of white powder as HBr salt of 2-amino-5-bromo-3-fluorobenzoic acid (95% yield). ES/MS *m/z* 234/236 (MH^+).

PP028218.0002

Step 2. To the above intermediate (30.6 mmol) in THF (100 mL) at 0 C was added boran tetrahydrofuran complex solution (1 M in THF, 129 mL, 4 equiv.). The mixture was stirred at room temperature for 40 hrs. The solvent was removed in vacuo and the excess reagent was quenched by addition of water (30 mL) slowly. The pH (~3) was adjusted by adding sodium bicarbonate (sat. aq.) to pH 7. Extracted with methylene chloride. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material as white solide. ES/MS *m/z* 220/222 (MH^+).

Step 3. To the above intermediate (30.6 mmol) in dichloromethane (450 mL) was added manganese dioxide (MnO_2, 22 g, 258 mmol). The mixture was stirred at room temperature under argon for 18 hrs. The mixture was filtered through celite pad and washed thoroughly with dichloromethane. The filtrated was concentrated in vacuo to give crude product (2-amino-5-bromo-3-fluorophenyl)methanol (5.6 g) which was used for the next step without further purification. ES/MS *m/z* 218/220 (MH^+).

Step 4. A mixture of (2-amino-5-bromo-3-fluorophenyl)methanol (5.6 g, 23.7 mmol, obtained from step 3) and urea (21 g, 15 equiv.) was heated to 175 °C with vigorous stirring for 15 min. The reaction was cooled to room temperature and water was added. The solid was collected by filtration. Air-dried to give 2-hydroxyquinazoline as a light brown solid.

Step 5. To the above crude material was added phosphooxychloride ($POCl_3$, 20 mL) and heated to 110 °C for 30 min. The resulting mixture was cooled to room temperature and concentrated in vacuo to nearly dryness. Ice water was added and pH was adjusted to ~6 using sodium bicarbonate. Extraction with dichloromethane followed by drying with sodium sulfate and concentrated in vacuo yielded desired product 6-bromo-2-chloro-8-fluoroquinazoline as light brown powder (1.63 g).

Example 11

Synthesis of 6-bromo-2,8-dichloroquinazoline

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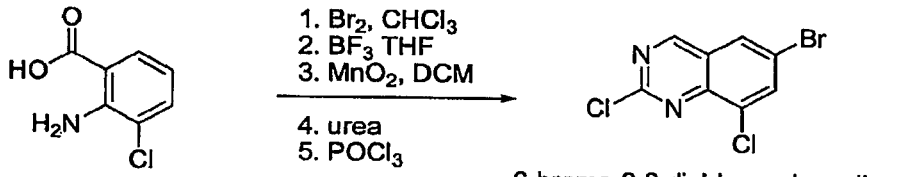


2-amino-3-chlorobenzoic acid

6-bromo-2,8-dichloroquinazoline

Step 1. To a suspension of 2-amino-3-chlorobenzoic acid (2 g, 11.6 mmol) in chloroform (120 mL) was added dropwise bromine (1.1 equiv.) in chloroform (12 mL) solution. The mixture was stirred at room temperature for 16 hrs. The resulting white solid was collected by filtration and washed thoroughly with methylene chloride until the filtrate was colorless. The solid was air-dried to give 3.35 g of white powder as HBr salt of 2-amino-5-bromo-3-chlorobenzoic acid (87% yield). ES/MS *m/z* 250/252 (MH^+).

Step 2. To the above intermediate (3.35 g, 10.1 mmol) in THF (40 mL) at 0 °C was added borane tetrahydrofuran complex solution (1 M in THF, 40 mL, 4 equiv.). The mixture was stirred at room temperature for 18 hrs. Additional borane tetrahydrofuran (20 mL) was added and continued reaction for another 24 hrs until the complete conversion of the starting material. The solvent was removed in vacuo and the excess reagent was quenched by addition of ethanol (20 mL) slowly. Water was added and the pH (~3) was adjusted by adding sodium bicarbonate (sat. aq.) to pH 7. Extracted with methylene chloride. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material as white solide. ES/MS *m/z* 236/238 (MH^+).

Step 3. To the above intermediate (10.1 mmol) in dichloromethane (80 mL) was added manganese dioxide (MnO_2, 6 g, 70 mmol). The mixture was stirred at room temperature under argon for 40 hrs. Additional manganese dioxide (6 g) was added and the reaction was continued for another 20 hrs until the complete conversion of the starting material. The mixture was filtered through celite pad and washed thoroughly with dichloromethane. The filtrated was concentrated in vacuo to give crude product (2-amino-5-bromo-3-chlorophenyl)methanol (3.3 g, orange solid) which was used for the next step without further purification. ES/MS *m/z* 234/236 (MH^+).

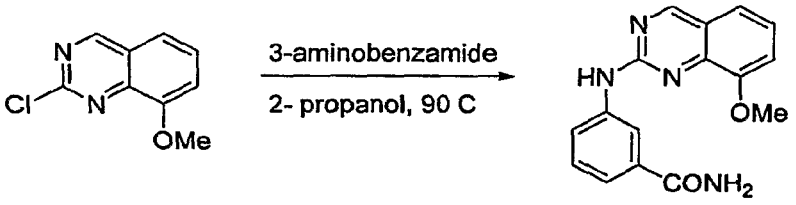
PP028218.0002

Step 4. A mixture of (2-amino-5-bromo-3-chlorophenyl)methanol (3.3 g, obtained from step 3) and urea (10.5 g, 15 equiv.) was heated to 180 °C with vigorous stirring for 1 hr. The reaction was cooled to room temperature and water was added. The solid was collected by filtration. Air-dried to give 2-hydroxyquinazoline as a yellow powder (2.18 g, crude). ES/MS *m/z* 259/261 (MH^+).

Step 5. To the above crude material was added phosphooxychloride ($POCl_3$, 25 mL) and heated to 130 °C for 30 min. The resulting mixture was cooled to room temperature and concentrated in vacuo to nearly dryness. Ice water was added and pH was adjusted to ~8 using sodium bicarbonate. Extraction with dichloromethane followed by drying with sodium sulfate and concentrated in vacuo yielded desired product 6-bromo-2,8-dichloroquinazoline as brown foam (1.4 g). This material was used in other chemical medications without further purification.

Example 12

Preparation of 3-(8-methoxyquinazolin-2-ylamino)benzamide



3-(8-methoxyquinazolin-2-ylamino)benzamide

To a 0.30 M solution of 2-chloro-8-methoxyquinazoline in 2-propanol was added 3-aminobenzamide (1.0 eq). The reaction was stirred at 90 °C for 14 h. The resulting solid was collected by vacuum filtration and triturated with additional 2-propanol. The yellow solid was dried in a desiccator to give the desired product as the hydrochloride. Alternatively, the product could be purified by reverse-phase HPLC and lyophilized to give the desired product as the trifluoroacetic acid salt. ES/MS *m/z* 295 (MH^+).

Example 13

Preparation of N-(3,5-dimethoxyphenyl)-8-methoxyquinazolin-2-amine

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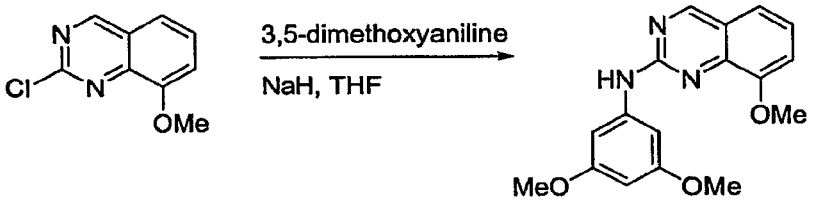
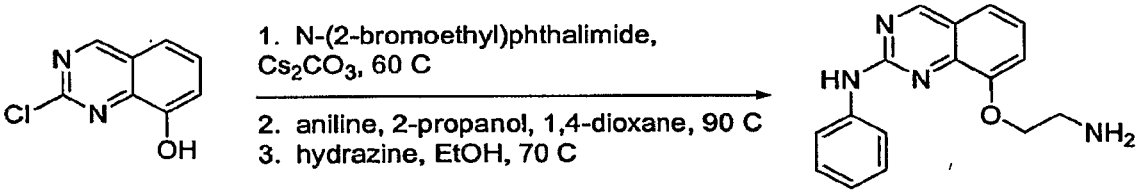


N-(3,5-dimethoxyphenyl)-8-methoxyquinazolin-2-amine

To a 0.40 M suspension of sodium hydride (2.0 eq) in THF was added 3,5-dimethoxyaniline (2.0 eq). The mixture was stirred for 10 min. 2-Chloro-8-methoxyquinazoline was added. The reaction was stirred for 2 h at ambient temperature and then quenched with water. The mixture was concentrated and purified by reverse-phase HPLC and lyophilized to give the desired product as the trifluoroacetic acid salt. ES/MS *m/z* 312 (MH^+).

Example 14

Preparation of 8-(2-aminoethoxy)-N-phenylquinazolin-2-amine (Compound 507)



8-(2-aminoethoxy)-*N*-phenylquinazolin-2-amine

Step 1. Preparation of 8-O-alkylated intermediate

To a 0.20 M suspension of 2-chloroquinazolin-8-ol (1.0 eq) in THF was added cesium carbonate (4.0 eq). The mixture was stirred for 5 min at ambient temperature. N-(2-bromoethyl)phthalimide was added. The reaction was stirred for 24 h at 60 C. The mixture was diluted with THF and DCM, filtered, and concentrated. The crude material was purified by flash chromatography (1:1:1 hexanes : ethyl acetate : DCM) to give the desired product. ES/MS *m/z* 354 (MH^+).

Step 2. Preparation of 2-anilino intermediate

PP028218.0002

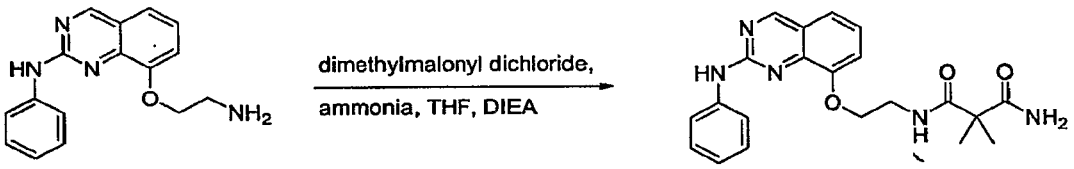
To a 0.20 M suspension of the product from Step 1 (1.0 eq) in 3:1 2-propanol:1,4-dioxane was added aniline (1.0 eq). The mixture was stirred at 90 C for 16 h and then concentrated to give the desired product as the hydrochloride salt. ES/MS *m/z* 411 (MH^+).

Step 3. Preparation of 8-(2-aminoethoxy)-N-phenylquinazolin-2-amine

To a 0.040 M suspension of the product from Step 2 (1.0 eq) in ethanol was added hydrazine (4.0 eq). The mixture was stirred at 70 C for 3 h and then concentrated. The residue was re-dissolved in chloroform and washed with water. The organic phase was dried over sodium sulfate, filtered, and concentrated. The material could be purified by reverse-phase HPLC and lyophilized to give the desired product as the trifluoroacetic acid salt. ES/MS *m/z* 281 (MH^+).

Example 15

Preparation of 2,2-dimethyl-N1-(2-(2-(phenylamino)quinazolin-8-yloxy)ethyl)malonamide (Compound 508)



2,2-dimethyl-N^1-(2-(2-(phenylamino)quinazolin-8-yloxy)ethyl)malonamide

To a 0.11M solution of dimethylmalonyl dichloride (2.0 eq) in THF was added a 0.5 M solution of ammonia in dioxane (3.5 eq). The mixture was stirred for 15 min at ambient temperature. Crude 591475 was added. After stirring for 5 min, DIEA (4.0 eq) was added; and the mixture was stirred for 30 min. Volatiles were removed under reduced pressure, and the crude residue was purifed by reverse-phase HPLC and lyophilized to give the desired product as the trifluoroacetic acid salt. ES/MS *m/z* 394 (MH^+).

Example 16

Preparation of 4-(8-isopropoxyquinazolin-2-ylamino)-N-methylbenzamide (Compound 515)

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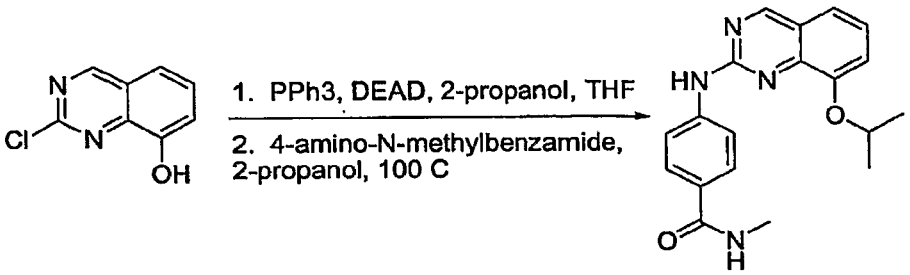


4-(8-isopropoxyquinazolin-2-ylamino)-*N*-methylbenzamide

Step 1. Preparation of 8-O-alkylated intermediate

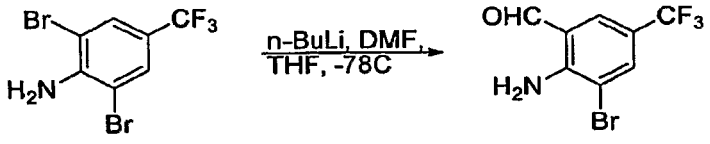
To a 0.30 M solution of triphenylphosphine (1.5 eq) in THF was added diethylazodicarboxyate (1.5 eq). The mixture was stirred 15 min at ambient temperature. 2-Propanol (4.0 eq) was added. The mixture was stirred 15 min at ambient temperature. 2-Chloroquinazolin-8-ol (1.0 eq) was added. The mixture was stirred an additional 4 h. The crude mixture was concentrated, purified by flash chromatography (3:1 hexanes : ethyl acetate) to give the desired product. ES/MS *m/z* 223 (MH^+).

Step 2. Preparation of 4-(8-isopropoxyquinazolin-2-ylamino)-N-methylbenzamide

To a 0.30 M solution of the product from Step 1 in 2-propanol was added 4-amino-N-methylbenzamide (1.0 eq). The reaction was stirred at 100 °C for 14 h. The mixture was concentrated and purified by reverse-phase HPLC and lyophilized to give the desired product as the trifluoroacetic acid salt. ES/MS *m/z* 337 (MH^+).

Example 17

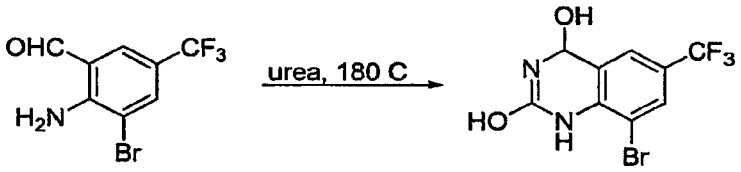
Preparation of 4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide (Compound 963)



Step 1. Preparation of 2-Amino-3-bromo-5-(trifluoromethyl)benzaldehyde

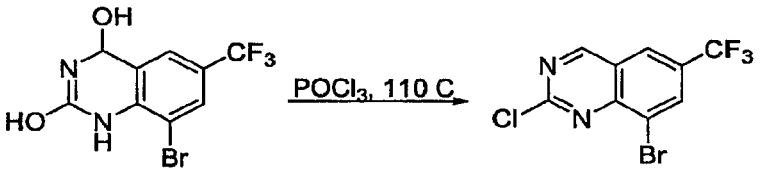
2,6-Dibromo-4-(trifluoromethyl)aniline (3.19 g, 10.0 mmol, 1.00 eq) was dissolved in THF (50 mL) and cooled to –78 °C. A 2.5 M solution of n-butyllithium in hexanes (8.40 mL, 21.0 mmol,

2.10 eq) was added dropwise over 15 min. The mixture was stirred at -78 °C for 1 h. A solution of DMF (1.03 mL, 14.0 mmol, 1.40 eq) in THF (5 mL) was added, and the mixture was stirred an additional 1 h at –78 °C. The reaction was allowed to come to –15 °C over 30 min and then quenched with brine. The mixture was diluted with ethyl acetate, washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated to give 1.74 g of the desired product as a pale yellow, crystalline solid. ES/MS *m/z* 268,270 (MH^+).



Step 2. Preparation of 8-bromo-6-(trifluoromethyl)-1,4-dihydroquinazoline-2,4-diol

2-Amino-3-bromo-5-(trifluoromethyl)benzaldehyde (1.74 g, 6.49 mmol, 1.00 eq) and urea (5.85 g, 97.4 mmol, 15.0 eq) were stirred at 190 °C for 3 h. The resulting solid was returned to ambient temperature, stirred in water (60 mL) for 20 min, and filtered. This was repeated for a total of three washes. The solid was dried in a desiccator to give 3.79 g of the desired product as an off-white solid. ES/MS *m/z* 311,313 (MH^+).



Step 3. Preparation of 8-Bromo-2-chloro-6-(trifluoromethyl)quinazoline

8-Bromo-6-(trifluoromethyl)-1,4-dihydroquinazoline-2,4-diol (3.79 g, 6.49 mmol, 1.00 eq). Phosphorus oxychloride (20 mL) was added. The mixture was stirred at 110 °C for 1.5 h. Volatiles were removed under reduced pressure. Ice water was added, and the pH was adjusted to 6-7 with aqueous sodium hydroxide and sodium bicarbonate. The precipitate was filtered off, rinsed with water, and dried under high vacuum. The crude material was triturated with THF. The mother liquor was concentrated to yield 332 mg of the desired product as an orange, crystalline solid. ES/MS *m/z* 313 (MH^+).

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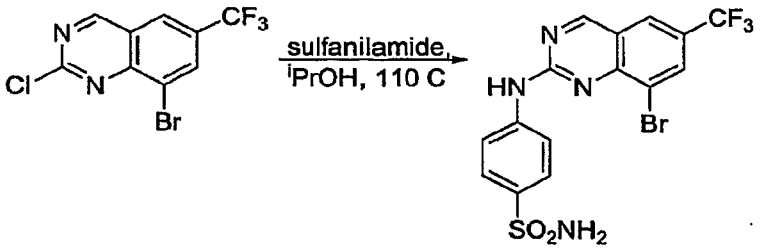
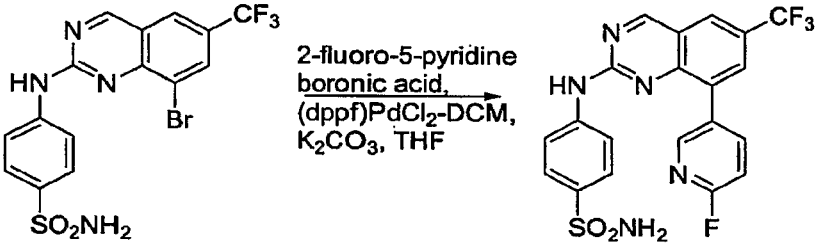


Step 4. Preparation of 4-(8-bromo-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide

To a 0.30 M solution of 8-bromo-2-chloro-6-(trifluoromethyl)quinazoline in 2-propanol was added sulfanilamide (1.0 eq). The reaction was stirred at 110 °C for 14 h. The hydrochloride was collected by vacuum filtration and then stirred in aqueous sodium bicarbonate. The solid was collected by vacuum filtration and rinsed with water. The light yellow solid was dried in a desiccator to give 343 mg of the desired product. ES/MS *m/z* 447,449 (MH^+).



Step 5. Preparation of 4-(8-(6-fluoropyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide

To a 0.050 M solution of 4-(8-bromo-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide (1.0 eq) in DME was added 2-fluoro-5-pyridineboronic acid (3.0 eq), (dppf)Pd(II)Cl_2-CH_2Cl_2 (0.050 eq) and 2M aqueous potassium carbonate (8.0 eq). The mixture was microwaved at 120 °C for 10 min and then diluted with ethyl acetate and filtered through a pad of silica gel. The filtrate was concentrated to give the desired product which was used without further purification. ES/MS *m/z* 464 (MH^+).

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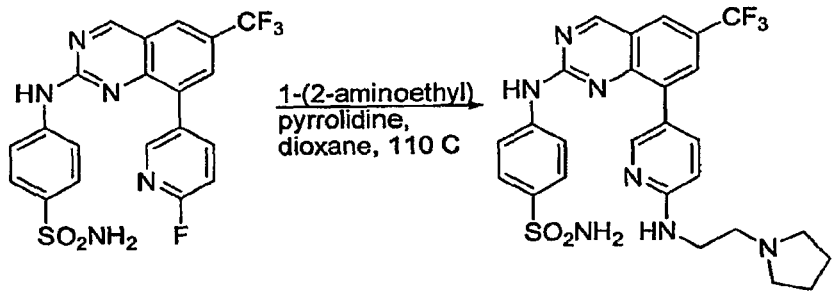


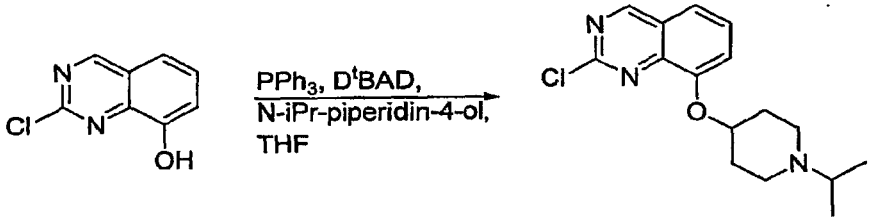
4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide

Step 6. Preparation of 4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)pyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide

To a 0.25M solution of 4-(8-(6-fluoropyridin-3-yl)-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide (1.0 eq) in dioxane was added 1-(2-aminoethyl)pyrrolidine (3.0 eq). The mixture was stirred at 110 °C for 14 h and then concentrated and purified by reverse phase HPLC to give the desired compound as its TFA salt. ES/MS *m/z* 558 (MH^+).

Example 18

Synthesis of 2-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-methylacetamide (Compound 969)



2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline

Step 1. Preparation of 2-Chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline

To a 0.30M solution of triphenylphosphine (1.5 eq) in THF was added di-tert-butylazodicarboxylate (1.5 eq). The mixture was stirred 15 min at ambient temperature. 4-Hydroxy-1-isopropylpiperidine (4.0 eq) was added. The mixture was stirred 15 min at ambient temperature. 2-Chloroquinazolin-8-ol (1.0 eq) was added. The mixture was stirred an additional 2 h. The crude mixture was concentrated, purified by flash chromatography (EtOAc then 90:10:1 DCM:MeOH:NH_4OH), and concentrated to give the desired product in 88% yield. ES/MS *m/z* 306 (MH^+).

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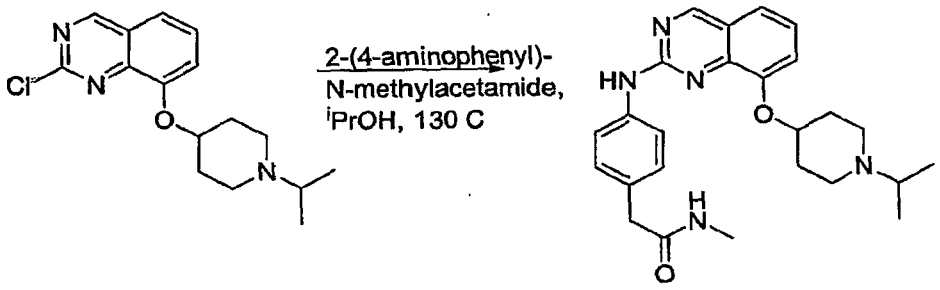


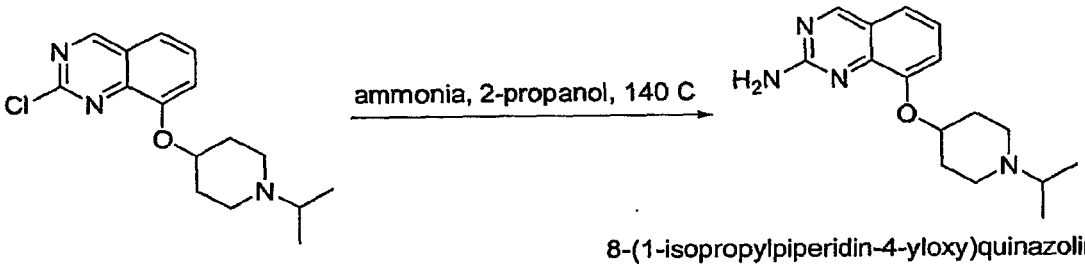
2-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-*N*-methylacetamide

Step 2. Preparation of 2-(4-(8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-ylamino)phenyl)-N-methylacetamide

To a 0.50M solution of 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in 2-propanol was added 2-(4-aminophenyl)-N-methylacetamide(1.0 eq). The reaction was stirred at 130 °C for 14 h. The crude mixture was concentrated, purified by reverse-phase HPLC, and lyophilized to give the desired product as a TFA salt. ES/MS *m/z* 434 (MH^+).

Example 19

Preparation of 8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine



8-(1-isopropylpiperidin-4-yloxy)quinazolin-2-amine

Ammonia was bubbled into a 0.50M solution of 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline (1.0 eq) in 2-propanol. The reaction was stirred at 140 °C for 4 d in a sealed vessel. The crude mixture was concentrated, purified by reverse-phase HPLC, and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 287 (MH^+).

Example 20

Synthesis of morpholino(4-(8-(piperidin-4-yloxy)quinazolin-

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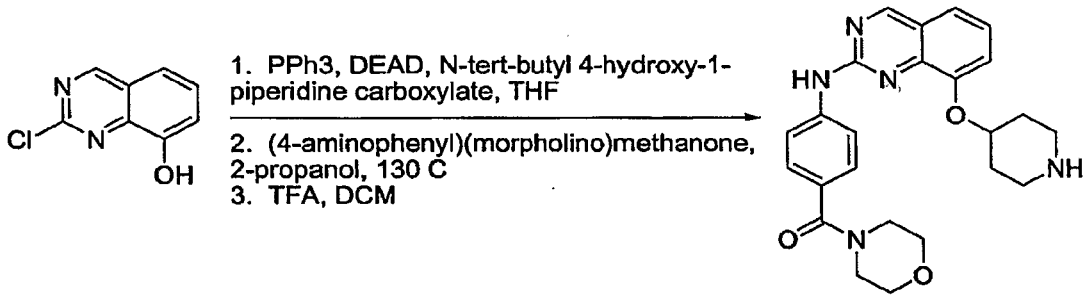
2-ylamino)phenyl)methanone (Compound 538)



morpholino(4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)methanone

Step 1. Preparation of 2-Chloro-8-(N-Boc-piperidin-4-yloxy)quinazoline

To a 0.30 M solution of triphenylphosphine (1.5 eq) in THF was added diethylazodicarboxylate (1.5 eq). The mixture was stirred 15 min at ambient temperature. N-Tert-butyl-4-Hydroxy-1-piperidine carboxylate (4.0 eq) was added. The mixture was stirred 15 min at ambient temperature. 2-Chloroquinazolin-8-ol (1.0 eq) was added. The mixture was stirred an additional 4 h. The crude mixture was concentrated, purified by flash chromatography (3:2 hexanes:EtOAc), and concentrated to give the desired product. ES/MS *m/z* 364 (MH^+).

Step 2. Displacement

To a 0.50M solution of 2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline in 2-propanol was added (4-aminophenyl)(morpholino)methanone (1.0 eq). The reaction was stirred at 130 °C for 14 h. The crude mixture was concentrated and used without further purification. ES/MS *m/z* 534 (MH^+).

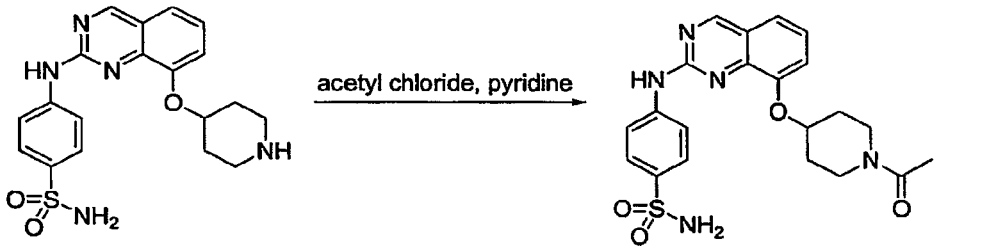
Step 3. Preparation of morpholino(4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)phenyl)methanone

The product from Step 2 was dissolved in enough 1:1 DCM:TFA to make a 0.20M solution. The mixture was stirred for 30 min at ambient temperature and concentrated. The crude product was purified by reverse-phase HPLC and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 434 (MH^+).

PP028218.0002

Example 21

Preparation of 4-(8-(1-acetylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide (Compound 539)

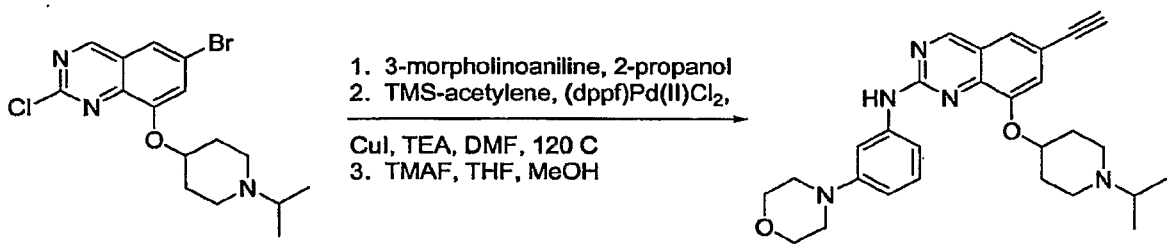


4-(8-(1-acetylpiperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide

To a 0.33M solution of 4-(8-(piperidin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide in pyridine was added acetyl chloride (1.5 eq). The reaction was stirred for 2 h at ambient temperature and quenched with water. The crude mixture was concentrated, purified by reverse-phase HPLC, and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 442 (MH^+).

Example 22

Synthesis of 6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)-N-(3-morpholinophenyl)quinazolin-2-amine (Compound 697)



6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)-*N*-(3-morpholinophenyl)quinazolin-2-amine

Step 1. Displacement of 2-chloro

To a 0.25M solution of 3-morpholinoaniline in 2-propanol was added 6-bromo-2-chloro-8-(1-isopropylpiperidin-4-yloxy)quinazoline (prepared by following Example 9, step 2). The mixture

PP028218.0002

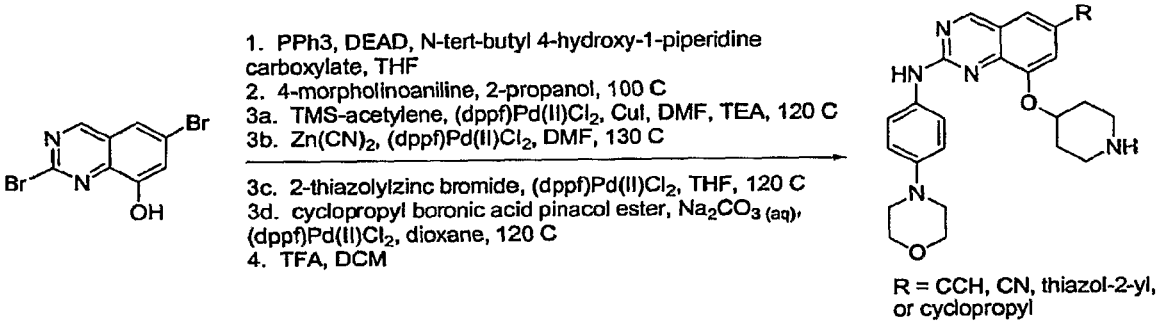
was stirred at 120 °C for 14 h, concentrated, and used without further purification. ES/MS *m/z* 526,528 (MH^+).

Step 2-3. Preparation of 6-ethynyl-8-(1-isopropylpiperidin-4-yloxy)-N-(3-morpholinophenyl)quinazolin-2-amine

The product of step 1 was subjected to subjected to Sonogashira and desilylation reaction (see the scheme above) to give the title compound. ES/MS *m/z* 306 (MH^+).

Example 23

Preparation of 6-ethynyl-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine (Compound 700)



Step 1. Preparation of 2,6-dibromo -8-(N-Boc-piperidin-4-yloxy)quinazoline

To a 0.30M solution of triphenylphosphine (2.0 eq) in THF was added diethylazodicarboxylate (2.0 eq). The mixture was stirred 15 min at ambient temperature. N-Tert-butyl-4-Hydroxy-1-piperidine carboxylate (4.0 eq) was added. The mixture was stirred 15 min at ambient temperature. 2,6-Dibromo-8-hydroxyquinazoline (1.0 eq) was added. The mixture was stirred an additional 24 h. The crude mixture was concentrated, purified by flash chromatography (2:1 hexanes:EtOAc), and concentrated to give the desired product. ES/MS *m/z* 488 (MH^+).

Step 2. Displacement

To a 0.50M solution of 2,6-dibromo-8-(N-Boc-piperidin-4-yloxy)quinazoline in 2-propanol was added 4-morpholinoaniline (1.0 eq). The reaction was stirred at 100 °C for 14 h. The crude mixture was concentrated and used without further purification. ES/MS *m/z* 584,586 (MH^+).

PP028218.0002

Step 3a. Sonogashira & desilylation

The product from Step 2 was subjected to Sonogashira and desilylation reaction (see the scheme above) and carried on to Step 4 without purification. ES/MS *m/z* 530 (MH^+).

Step 3b. Cyanation

The product from Step 2 was subjected to cyanation reaction (see the scheme above) and carried on to Step 4 without purification. ES/MS *m/z* 531 (MH^+).

Step 3c. Negishi

The product from Step 2 was subjected to Negishi reaction (see the scheme above) and carried on to Step 4 without purification. ES/MS *m/z* 589 (MH^+).

Step3d. Suzuki

To a 0.10M solution of the product from Step 2 (1.0eq) in 1,4-dioxane was added cyclopropyl boronic acid pinacol ester (4.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.20 eq), and 2.0M aqueous sodium carbonate (7.0 eq). The reaction was microwaved at 140 °C for 10 min. The mixture was diluted with THF, filtered, concentrated, and carried on to Step 4 without purification. ES/MS *m/z* 488 (MH^+).

Step 4. Preparation of 6-ethynyl-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine

The product from Step 3 was dissolved in enough 1:1 DCM:TFA to make a 0.20M solution. The mixture was stirred for 30 min at ambient temperature and concentrated. The crude product was purified by reverse-phase HPLC and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 430 (MH^+).

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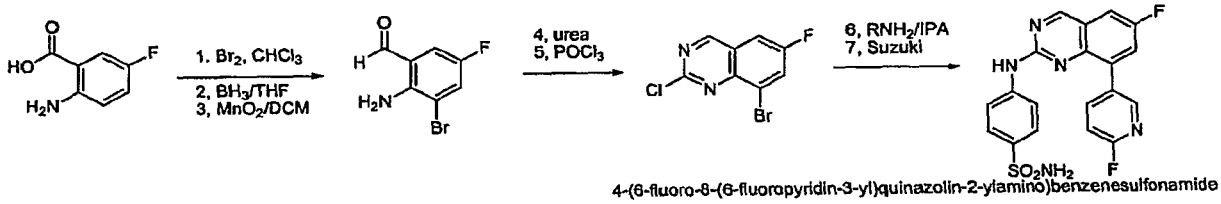
Example 24

Synthesis of 4-(6-fluoro-8-(6-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide (Compound 633)



Step 1. To 2-Amino-5-fluorobenzoic acid (5 g, 32.2 mmol) in chloroform (90 mL) was added bromine (1.82 mL, 35.4 mmol) in chloroform (10 mL) solution dropwise via an additional funnel. The mixture was stirred at room temperature for 16 hrs. and LC/MS showed about 50% conversion of the starting material. Additional bromine (1.8 mL) was added to the reaction and continued stirring for another 24 hrs. The resulting white precipitate was collected by filtration, washed thoroughly with dichloromethane and air-dried to give 2-amino-3-bromo-5-fluorobenzoic acid as its HBr salt. ES/MS *m/z* 234/236 (MH^+).

Step 2. (2-Amino-3-bromo-5-fluorophenyl)metanol
To a 0.5M suspension of 2-amino-3-bromo-5-fluorobenzoic acid in THF in an ice bath was slowly added borane (1.0M /THF, 3eq). The reaction mixture was stirred at ambient temperature for 24 h. The mixture was recooled to 0°C and quenched with methanol and concentrated to remove solvent. The residue was taken into ethyl acetate and organic phase was washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated to give yellow solid in 90% yield. ES/MS *m/z* 220/222 (MH^+).

Step 3. 2-Amino-3-bromo-5-fluorobenzaldehyde
Manganese (IV) oxide (5eq) was added to a 0.2M solution of (2-amino-3-bromo-5-fluorophenyl)methanol in dichloromethane. The suspension was stirred at ambient temperature under Argon for 12 h. The reaction mixture was filtered through celite and filter cake was washed with dichloromethane. The combined filtrate was concentrated to give brown color solid. ES/MS *m/z* 218/220 (MH^+).

PP028218.0002

Step 4. 8-Bromo-6-fluoroquinazolin-2-ol

Solid 8-bromo-6-fluoroquinazolin-2-ol (1eq) and urea (14eq) were thoroughly mixed together in a round bottom flask. The mixture was heated to 180 °C in an oil bath for 2.5 h. The reaction mixture was cooled to ambient temperature and water was added to the flask. Filtration gave yellow color solid, which was rinsed with ether and air dried. Yield: 62%. ES/MS *m/z* 243/245 (MH^+).

Step 5. 8-Bromo-2-chloro-6-fluoroquinazoline

A 0.5M suspension of 8-bromo-6-fluoroquinazolin-2-ol in phosphorus oxychloride was heated to 110 °C in an oil bath. The suspension was turned to a brown color solution in 20min. LCMS data showed that the reaction was complete after 1 h. The phosphorus oxychloride was removed by concentration. The residue was mixed with ice water, and adjusted pH to 7 by adding sodium bicarbonate. Reaction mixture was extracted with ethyl acetate. Combined organic phase was washed with water, brine, dried over sodium sulfate and concentrated to give desired product in 89% yield. ES/MS *m/z* 261/263 (MH^+).

Step 6. 4-(8-Bromo-6-fluoroquinazolin-2-ylamino)benzensulfonamide

To a 0.4M suspension of 8-bromo-2-chloro-6-fluoroquinazoline in isopropanol was added 4-aminobenzensulfonamide (1eq). The reaction mixture was heated to 120 °C in an oil bath for 2days. LCMS showed that reaction was complete under the condition. Ethyl acetate was added to the reaction flask and the suspension was stirred at ambient temperature for 30 min and was filtered. Filter cake was rinsed with hexane and dried in vacuum to give product in 81% yield. ES/MS *m/z* 397/399 (MH^+).

Step 7. Preparation of 4-(6-fluoro-8-(6-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide

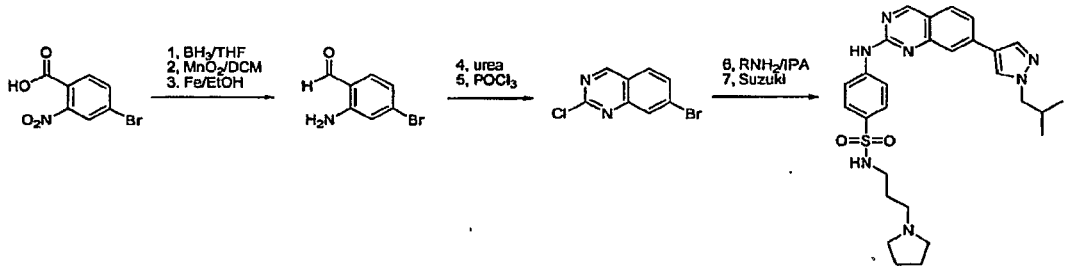
Pd(dppf)2Cl2CH2Cl2 (0.05eq) was added to a 0.1M mixture of 4-(8-bromo-6-fluoroquinazolin-2-ylamino)benzensulfonamide (1eq), 6-fluoropyridin-3-ylboronic acid (3eq), potassium carbonate/water (2.0M, 2eq) in DME. The mixture was microwaved at 120 °C for 20min. Reaction mixture was diluted with ethyl acetate and washed with water, brine, dried and

PP028218.0002

concentrated. The crude product was purified by RP HPLC. Lyophilization gave desired product 596148. ES/MS *m/z* 414 (MH^+).

Example 25

Synthesis of 4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(3-(pyrrolidin-1-yl)propyl)benzenesulfonamide (Compound 709)



4-(7-(1-isobutyl-1*H*-pyrazol-4-yl)quinazolin-2-ylamino)-*N*-(3-(pyrrolidin-1-yl)propyl)benzenesulfonamide

Step1. (4-Bromo-2-nitrophenyl)methanol

To a 0.5M suspension of 4-bromo-2-nitrobenzoic acid in THF in an ice bath was slowly added borane (1.0M /THF, 4eq). The reaction mixture was stirred at ambient temperature for 48 h. LCMS showed the reaction was complete. The mixture was recooled to 0°C and quenched with methanol and concentrated to remove solvent. The residue was taken into ethyl acetate and organic phase was washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated to give yellow solid in 95% yield.

Step 2. 4-Bromo-2-nitrobenzaldehyde

Manganese (IV) oxide (4eq) was added to a 0.18M solution of (4-bromo-2-nitrophenyl)methanol in dichloromethane. The suspension was stirred at ambient temperature under Argon for 12 h. The reaction mixture was filtered through celite and filter cake was washed with dichloromethane. The combined filtrate was concentrated to give brown color solid in 78% yield.

Step 3. 2-Amino-4-bromobenzaldehyde

To a 0.2M solution of 4-bromo-2-nitrobenzaldehyde in acetic acid and ethanol (v/v 1:1) solvent system was added iron powder. The reaction mixture was stirred at ambient temperature under

PP028218.0002

Argon for 1.5 h and LCMS showed the reaction was complete. Insoluble solid was filtered off and the filtrate was concentrated in vacuum. Residue was diluted with ethyl acetate and was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Crude product was purified by Biotage using 15% ethyl acetate in hexane to give desired product in 38% yield. ES/MS *m/z* 200/202 (MH^+).

Step 4. 7-Bromoquinazolin-2-ol

A mixture of 2-amino-4-bromobenzaldehyde (1eq) and urea (14eq) was heated to 180 °C in an oil bath under Argon for 1 h. Water was added to after cooling to ambient temperature. The solid was collected by filtration and air dried to give product in 95% yield. ES/MS *m/z* 225/227 (MH^+).

Step 5. 7-Bromo-2-chloroquinazoline

A 0.5M suspension of 7-bromoquinazolin-2-ol in phosphorus oxychloride was heated to 110 °C in an oil bath for 1 h. The mixture was cooled to room temperature. Volatiles were removed under reduced pressure. The residue was triturated with ice water. The solid was collected by filtration and air dried to give product in 65% yield. ES/MS *m/z* 243/245 (MH^+).

Step 6. 4-(7-Bromoquinazolin-2-ylamino)-N-(3-(pyrrolidin-1-yl)propyl) benzenesulfonamide

To a 0.1M suspension of 7-bromo-2-chloroquinazoline in isopropanol was added 4-amino-N-(3-(pyrrolidin-1-yl)propyl)benzenesulfonamide (1.1eq), followed by the addition of 4.0M HCl in dioxane (1.1eq) . The reaction mixture was heated to 120 °C in an oil bath for 1 h. LCMS showed that reaction was complete under the condition. Ethyl acetate was added to the reaction flask and the mixture was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Desired product was a yellow color solid. ES/MS *m/z* 490/492 (MH^+).

Step 7. Preparation of 4-(7-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)-N-(3-(pyrrolidin-1-yl)propyl)benzenesulfonamide

Pd(dppf)2Cl2CH2Cl2 (0.05eq) was added to a 0.05M mixture of 4-(7-bromoquinazolin-2-ylamino)-N-(3-(pyrrolidin-1-yl)propyl) benzenesulfonamide (1eq), 1-isobutyl-4-(4,4,5,5-

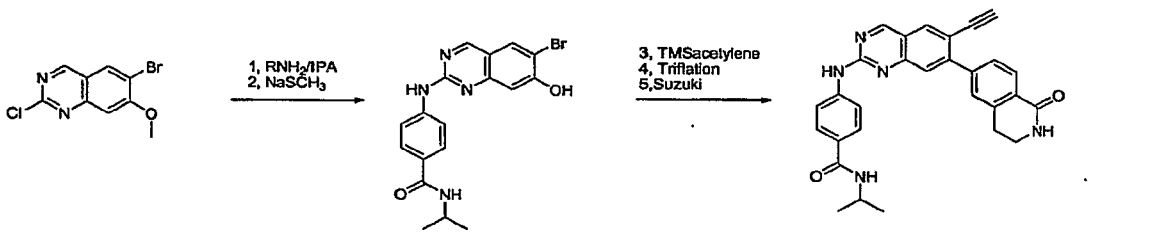
PP028218.0002

tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3eq), 2.0M potassium carbonate/water (2eq) in DME. The mixture was microwaved at 120 °C for 10min.

Reaction mixture was diluted with ethyl acetate and washed with water, brine, dried and concentrated. The crude product was purified by RP HPLC. Lyophilization gave desired product. ES/MS *m/z* 534 (MH^+).

Example 26

Synthesis of 4-(6-ethynyl-7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)-N-isopropylbenzamide



4-(6-ethynyl-7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)-*N*-isopropylbenzamide

Step 1. 4-(6-Bromo-7-methoxyquinazolin-2-ylamino)-N-isopropylbenzamide

To a 0.25M suspension of 6-bromo-2-chloro-7-methoxyquinazoline in isopropanol was added 4-amino-N-isopropylbenzamide (1.0eq). The reaction mixture was heated to 100 °C in an oil bath for 14 h. Reaction mixture was diluted with ethyl acetate and filtered to collect desired product. ES/MS *m/z* 415/417 (MH^+).

Step 2. 4-(6-Bromo-7-hydroxyquinazolin-2-ylamino)-N-isopropylbenzamide

A 0.15M suspension of 4-(6-bromo-7-methoxyquinazolin-2-ylamino)-N-isopropylbenzamide (1.0eq) and sodium thiomethoxide (4.0eq) in DMF was heated to 80 °C in an oil bath for 12 h. The mixture was partitioned between ethyl acetate and water. The pH of aqueous phase was adjusted to 5 by adding saturated ammonium hydrochloride. Aqueous phase was extracted with ethyl acetate, and combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to give desired product in 90% yield. ES/MS *m/z* 401/403 (MH^+).

PP028218.0002

Step 3. 4-(7-Hydroxy-6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)-N-isopropylbenzamide
To a 0.09M mixture of 4-(6-bromo-7-hydroxyquinazolin-2-ylamino)-N-isopropylbenzamide (0.17 mM), triethylamine (0.5ml), Pd(dppf)2Cl2CH2Cl2 (0.1eq), Copper(I) iodide (0.1eq), in DMF was added trimethylsilylacetylene (10eq).The suspension was microwaved at 120 °C for 20min. Reaction mixture was diluted with ethyl acetate and was washed with water, brine, dried and concentrated to give crude product. ES/MS *m/z* 419 (MH^+).

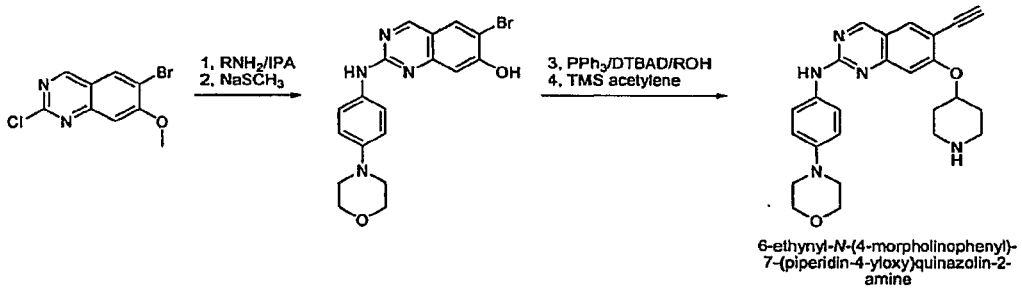
Step 4. 2-(4-(Isopropylcarbamoyl)phenylamino)-6-((trimethylsilyl)ethnyl)quinazolin-7-yltrifluoromethanesulfonate
To a 0.15M solution of 4-(7-hydroxy-6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)-N-isopropylbenzamide in NMP were added N-phenyl-bis(trifluoromethanesulfonimide) (1.2eq), and N,N-diisopropylethylamine (2.5eq). The mixture was stirred at ambient temperature for 15 h. Solution was diluted with ethyl acetate and was washed with water, brine, dried over sodium sulfate and concentrated to give crude product. ES/MS *m/z* 551 (MH^+).

Step 5. Preparation of 4-(6-ethynyl-7-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)quinazolin-2-ylamino)-N-isopropylbenzamide
A 2.0M solution of potassium carbonate (0.8ml) was added to a mixture of 2-(4-(isopropylcarbamoyl)phenylamino)-6-((trimethylsilyl)ethnyl)quinazolin-7-yltrifluoromethanesulfonate (0.13 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-3,4-dihydroisoquinolin-1(2H)-one (0.38 mmol), Pd(dppf)2Cl2Ch2Cl2 (0.01 mmol) in 1,2-dimethoxyethane (4ml). The mixture was microwaved at 120 °C for 10min. LCMS indicated formation of Suzuki product. Mixture was diluted with ethyl acetate, and was washed with water, brine, dried and concentrated. The oil residue was treated with tetramethylammonium fluoride (30mg, 0.3 mmol) in THF (3ml) at ambient temperature for 1 h. Solvent was removed under reduced pressure, and residue was diluted with ethyl acetate. Organic phase was washed with water, brine, dried and concentrated. The crude product was purified by RP HPLC. Lyophilization gave desired product 623995. ES/MS *m/z* 476 (MH^+).

PP028218.0002

Example 27

Synthesis of 6-Ethynyl-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine (Compound 646)



Step 1. 6-Bromo-7-methoxy-N-(4-morpholinophenyl)quinazolin-2-amine

To a 0.12M suspension of 6-bromo-2-chloro-7-methoxyquinazoline (1.0eq) in isopropanol was added 4-morpholinoaniline (1.0eq). The reaction mixture was heated to 120 °C in an oil bath for 5 h. LCMS showed that reaction was complete under the condition. The reaction mixture was allowed to cool to room temperature and was filtered. The filter cake was rinsed with ethyl acetate and allowed air dry. Desired product was a brown solid as HCl salt. ES/MS *m/z* 415/417 (MH^+).

Step 2. 6-Bromo-2-(4-morpholinophenylamino)quinazolin-7-ol

A 0.32M suspension of 6-bromo-7-methoxy-N-(4-morpholinophenyl)quinazolin-2-amine (1.0eq) and sodium thiomethoxide (4.0eq) in DMF was heated to 80 °C in an oil bath for 12 h. LCMS data indicated the reaction was complete. The mixture was partitioned between ethyl acetate and water. The insoluble solid was filtered off and was rinsed with ether and air dried to give product. ES/MS *m/z* 401/403 (MH^+).

Step 3. tert-butyl 4-(6-bromo-2-(4-morpholinophenylamino)quinazolin-7-yloxy)piperidine-1-carboxylate

To a 0.07M solution of triphenylphosphine (3.0eq) in THF was added di-tert-butylazodicarboxylate (3.0eq). The mixture was stirred for 15 min at ambient temperature. N-Boc-4-hydroxypiperidine (3.0eq) was added, and the mixture was stirred at ambient temperature

PP028218.0002

for another 15 min. 6-Bromo-2-(4-morpholinophenylamino)quinazolin-7-ol (1.0eq, a 0.12M solution in THF) was added to reaction flask. The mixture was stirred an additional 15 h at ambient temperature. Solvent was removed under reduced pressure and the residue was purified by Biotage using 2% methanol in dichloromethane to give tert-butyl 4-(6-bromo-2-(4-morpholinophenylamino)quinazolin-7-yloxy)piperidine-1-carboxy. ES/MS *m/z* 584/586 (MH^+).

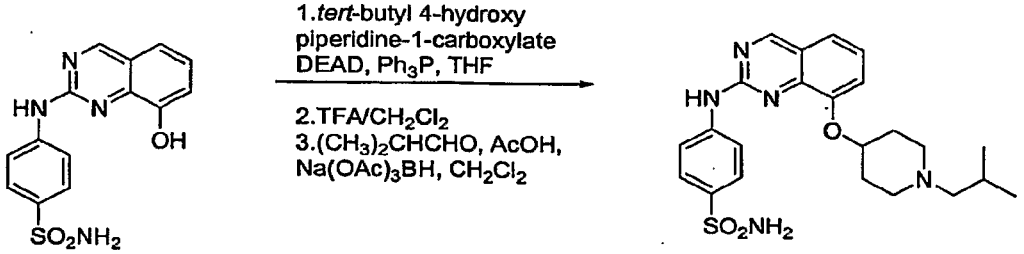
Step 4. Preparation of 624175 - 6-Ethynyl-N-(4-morpholinophenyl)-7-(piperidin-4-yloxy)quinazolin-2-amine

To a 0.05M mixture of tert-butyl 4-(6-bromo-2-(4-morpholinophenylamino)quinazolin-7-yloxy)piperidine-1-carboxylate (0.1 mmol), triethylamine (0.5ml), Pd(dppf)2Cl2CH2Cl2 (0.1eq), Copper(I) iodide (0.1eq), in DMF was added trimethylsilylacetylene (10eq).The suspension was microwaved at 120 °C for 25 min. Reaction mixture was diluted with ethyl acetate and was washed with water, brine, dried and concentrated. The oil residue was treated with tetramethylammonium fluoride (2.0eq) in THF/methanol (1:1, 0.05M) at ambient temperature for 1 h. Solvent was removed under reduced pressure. The residue was taken into ethyl acetate and was washed with water, brine, dried and concentrated. The resulting dark oil was treated with 50%TFA in dichloromethane at ambient temperature for 1 h. LCMS indicated De-Boc was complete. Solvent was removed under reduced pressure. The crude product was purified by RP HPLC. Lyophilization gave desired product 624175. ES/MS *m/z* 430 (MH^+).

Example 28

Preparation of 4-(8-(1-isobutylpiperidine-4-yloxy)quinazolin-2ylamino)benzene sulfonamide

The subject compound was prepared according to the general Scheme below:



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Step 1. Preparation of tert-butyl 4-(2-chloroquinazolin-8-yloxy)piperidine-1-carboxylate
To a solution of triphenylphosphine (2 eq) in THF was added di-ethyl-azodicarboxylate (2 eq). The mixture was stirred 15 minutes at ambient temperature. tert-butyl4-hydroxypiperidine-1-carboxylate (6 eq) was added. The mixture was stirred 15 minutes at ambient temperature. 4-(8-hydroxyquinazolin-2-ylamino)benzenesulfonamide (1.0 eq) was added. The mixture was stirred overnight at ambient temperature. The reaction goes to completion. The reaction mixture was concentrated and the oil was triturated the ether/hexane. A white solid crashed out. The solid was filtered to give tert-butyl 4-(2-chloroquinazolin-8-yloxy)piperidine-1-carboxylate in 90% yield ES/MS *m/z* 499 (MH^+).

Step 2. Preparation of 4-(8-(piperidine-4-yloxy)quinazolin-2ylamino)benzenesulfonamide
To a solution of tert-butyl-(2-chloroquinazolin-8-yloxy)piperidine-1-carboxylate in methylenechloride was added 30%TFA/ CH_2Cl_2 and the mixture was stirred for 1h to give the TFA salt of 4-(8-(piperidine-4-yloxy)quinazolin-2ylamino)benzenesulfonamide. The reaction mixture was concentrated to a solid to give the product in quantitative yield. ES/MS *m/z* 399 (MH^+)

Step 3. Preparation of 4-(8-(1-isobutylpiperidine-4-yloxy)quinazolin-2ylamino)benzenesulfonamide
To a solution of the TFA salt of 4-(8-(piperidin-4-yloxy)quinazoloin-2-ylamino)benzenesulfonamide in DCM was added isobutyraldehyde (2eq) and a few drops of acetic acid. The mixture was stirred for 10mins and to it was added sodiumtriacetoxyborohydride (1.5eq) and the mixture was stirred for 1h. The reductive amination went to completion. by LC/MS. The crude mixture was concentrated and purified on prep HPLC to give the product 4-(8-(1-isobutylpiperidine-4-yloxy)quinazolin-2ylamino)benzenesulfonamide in 80% yield. ES/MS *m/z* 456.2 (MH^+).

Example 29

Preparation of 4-(7-(6-morpholinopyridin-3yl)quinazolin-2ylamino-benzene sulfonamide (Compound 881)

The subject compound was prepared according to the general Scheme below:

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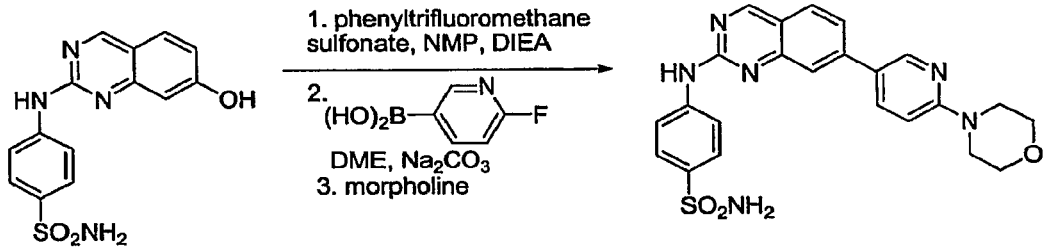


Step 1. Preparation of 2-(4-sulfamoylphenylamino) quinazolin-7-yltrifluoromethane sulfonate To a solution of 4-(7-hydroxyquinazolin-2-ylamino) benzenesulfonamide (1eq) in NMP was added phenyltrifluoromethanesulfonate (1.2eq) and DIEA (2.5eq) and the reaction mixture was stirred over night at ambient temperature. The reaction mixture was then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium chloride and dried and concentrated. To the crude was added methylene chloride and few drops of methanol. The white solid hence formed was filtered to give 2-(4-sulfamoylphenylamino)quinazolin-7-yltrifluoromethane sulfonate in 80% yield. ES/MS *m/z* 447(MH^+).

Step 2. Preparation of 4-(7-(6-fluoropyridin3-yl)quinazolin-2-ylamino)benzenesulfonamide. To a solution of 2-(4-sulfamoylphenylamino)quinazolin-7-yltrifluoromethane sulfonate (1eq) in DME was added 2M sodium carbonate solution and 6-fluoropyridin-3ylboronic acid (3eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was micro waved for 10 min at 120°C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was concentrated to yield 4-(7-(6-fluoropyridin3-yl)quinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 396(MH^+).

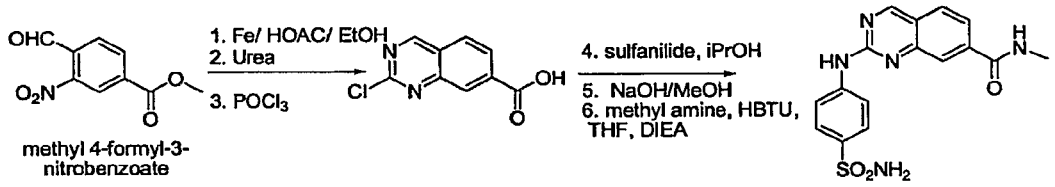
Step 3. Preparation of 4-(7-(6-morpholinopyridin-3yl)quinazolin-2ylamino-benzene sulfonamide To 4-(7-(6-fluoropyridin3-yl)quinazolin-2-ylamino)benzenesulfonamide was added morpholine. The solution was heated at 80°C for 3h. SNAR goes to completion and the product was purified on prep HPLC to yield 4-(7-(6-morpholinopyridin-3yl)quinazolin-2ylamino-benzene sulfonamide in 50% yield. ES/MS *m/z* 463(MH^+).

PP028218.0002

Example 30

Preparation of N-methyl-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of methyl 4-formyl-3-aminobenzoate

To a 1:1 mixture of ethanol and acetic acid was added methyl4-formyl-3-nitrobenzoate (1eq) and Fe dust (3eq) was added in portions. The reduction was complete in 1h. The reaction mixture was filtered and then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and dried and concentrated to give methyl 4-formyl-3-aminobenzoate in 85 % yield. ES/MS *m/z* 180(MH^+).

Step 2. Preparation of methyl 2-hydroxyquinazoin-7-carboxylate

To methyl 4-formyl-3-aminobenzoate(1eq) was added urea (5eq) and the mixture was heated to145°C for 16h. To the crude was added water and the precipitated solid was filtered to give methyl 2-hydroxyquinazoin-7-carboxylate in quantitative yield. ES/MS *m/z* 205(MH^+).

Step 3. Preparation of methyl 2-chloroquinazoin-7-carboxylate

To 2-hydroxyquinazoin-7-carboxylate was added $POCl_3$ and the mixture was added heated to 100°C for 20min when the reaction went to completion. To the reaction mixture was added ice and water and the precipitated solid was filtered and dried on the high vacuum overnight to give methyl 2-chloroquinazoin-7-carboxylate in 60% yield. ES/MS *m/z* 223(MH^+).

Step 4. Preparation of methyl 2-(4-sulfamoylphenylamino)quinazolin-7-carboxylate

To methyl 2-chloroquinazoin-7-carboxylate (1eq) was added sulfanilde (1eq) and isopropanol and the mixture was heated to 90°C for 2h. The reaction went to completion. The reaction

mixture was cooled to RT and filtered to give methyl 2-(4-sulfamoylphenyl amino)quinazolin-7-carboxylate in quantitative yield. ES/MS *m/z* 359(MH^+).

Step 5. Preparation of methyl 2-(4-sulfamoylphenylamino)quinazolin-7-carboxylic acid

To 2-(4-sulfamoylphenyl amino)quinazolin-7-carboxylate was added 2N sodium hydroxide (4eq) and methanol and the mixture was heated to 80°C for 10min. The saponification went to completion. The reaction mixture was concentrated and 1N HCl was added to precipitate methyl 2-(4-sulfamoylphenylamino)quinazolin-7-carboxylic acid as the HCl salt in quantitative yield. ES/MS *m/z* 344(MH^+).

Step 6. Preparation of N-methyl-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide

To methyl 2-(4-sulfamoylphenylamino)quinazolin-7-carboxylic acid (1eq) was added methylamine (2eq) and DIEA(4eq) and HBTU (2eq) and the mixture was stirred at RT overnight. The coupling went to completion and the mixture was concentrated and partitioned between ethyl acetate and water. The organic layers were concentrated and purified on the prep HPLC to give N-methyl-2-(4-sulfamoylphenylamino)quinazoline-7-carboxamide in 50% yield. ES/MS *m/z* 358(MH^+).

Example 31

Preparation of 7-(piperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine (Compound 569)

To tert-butyl 4-(2-(ethylsulfonyl)quinazolin-7-yloxy)piperidine-1-carboxylate (1eq) was added 3-trifluoromethylaniline and the mixture was heated to 100°C for 16h. The formation of the product was confirmed by LC/MS. The mixture was then partitioned between ethyl acetate and water. The organic layer was purified on prep HPLC to give tert-butyl 4-(2-(ethylsulfonyl)quinazolin-7-yloxy)piperidine-1-carboxylate. To the concentrated pure fractions was added 30% TFA/DCM. and the mixture was stirred for 30 min. The deprotection went to completion and the 7-(piperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine was isolated. ES/MS *m/z* 389(MH^+).

PP028218.0002

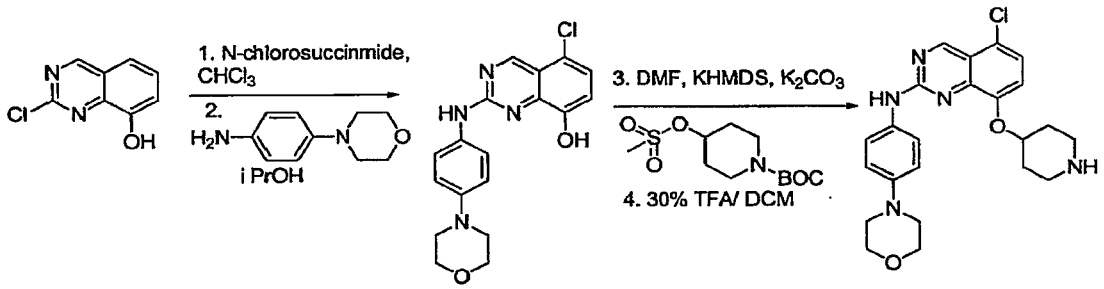
Preparation of 7-(1-isopropylpiperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl) quinazolin-2-amine (596754)

To 7-(piperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl)quinazolin-2-amine in DCM was added acetone (10eq), a few drops of acetic acid and sodium triacetoxy borohydride (4eq). The reaction mixture was stirred for 16h at ambient temperature. The reductive amination went to completion to give 7-(1-isopropylpiperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl) quinazolin-2-amine. The mixture was then purified on prep HPLC to give 7-(1-isopropylpiperidin-4-yloxy)-N-(3-(trifluoromethyl)phenyl) quinazolin-2-amine. ES/MS *m/z* 431(MH^+).

Example 32

Preparation of 5-chloro-N-(4-morpholinophenyl)-8-(piperidin-4-yloxy)quinazolin-2-amine (Compound 605)

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 2,5-dichloroquinazolin-8-ol

To a solution of 2-chloroquinazlin-8-ol (1eq) in chloroform was added N-chlosuccinimide (1eq) and the resulting mixture was heated to 40°C for 2h. The chlorination goes to completion giving 2,5-dichloroquinazalin-8-ol in 65 % yield. 25% of the reaction was 2,7dichloroquinazolin-8-ol and 15% of the reaction mixture was 2,5,8-trichloro quinazolin-8-ol. The reaction mixture was concentrated and the crude was purified by silica gel. The structures of the isomers were confirmed by ^{1}HNMR and by LC/MS. ES/MS *m/z* 215(MH^+).

PP028218.0002

Step 2. Preparation of 5-chloro-2-(4-morpholinophenylamino)quinazolin-8-ol
To a solution of isolated 2,5-dichloroquinazolin-8-ol (1eq) in isopropanol was added 4-morpholinoaniline (1eq) and the mixture was heated to 90°C for 1h. The SNAR went to completion by LC/MS and on concentration yielded 5-chloro-2-(4-morpholinophenylamino) quinazolin-8-ol in quantitative yield. ES/MS *m/z* 357(MH^+).
3. Preparation of tert-butyl 4-(5-chloto-2-(4-morpholinophenylamino)quinazolin-8-yloxy)piperidin-1-carboxylate.

Step 3. The tert-butyl4-(methylsulfonyloxy)piperidine-1-carboxylate used in this step was made as follows:
To tert-butyl 4-hydroxypiperidine-1-carboxylate (1eq) in methylene chloride and triethyl amine (1.4eq) at 0°C was added methane sulfonyl chloride (1.4 eq) drop-wise. The reaction was brought to ambient temperature and was stirred for 1h. The reaction mixture was washed with water and saturated sodium chloride solution. The organic layer was then dried with sodium sulfate and concentrated to yield tert-butyl4-(methylsulfonyloxy)piperidine-1-carboxylate in quantitative yield. The product was confirmed by ^1H NMR. and used without further purification.

To 5-chloro-2-(4-morpholinophenylamino)quinazolin-8-ol (1eq) in DMF was added potassium carbonate (1.1 eq) and KHMDS (1.2eq) and tert-butyl4-(methylsulfonyloxy)piperidine-1-carboxylate (1.5eq). The reaction mixture was micro waved at 170°C for 10min. Formation of tert-butyl 4-(5-chloto-2-(4-morpholinophenylamino)quinazolin-8-yloxy)piperidin-1-carboxylate was confirmed by LC/MS. ES/MS *m/z* 540(MH^+).

Step 4. Preparation of 5-chloro-N-(4-morpholinophenyl)-8-(piperidin-4yloxy)quinazolin-2-amine
The crude reaction mixture of tert-butyl 4-(5-chloto-2-(4-morpholinophenylamino) quinazolin -8-yloxy)piperidin-1-carboxylate was purified using prep HPLC and the purified fractions of the product was concentrated. To it was added a few drops of 30% TFA/ DCM and the mixture was stirred for 30 min. The deprotection went to completion yielding 5-chloro-N-(4-

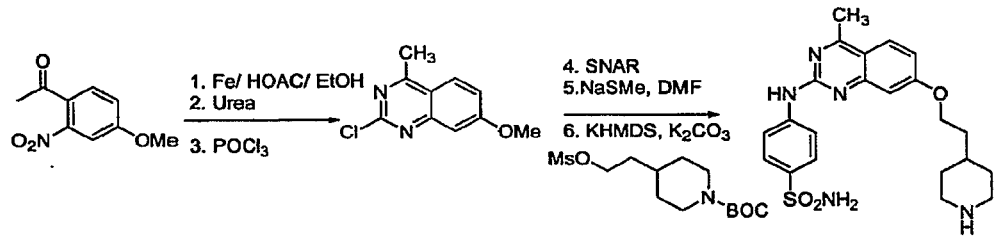
PP028218.0002

morpholinophenyl)-8-(piperidin-4yloxy)quinazolin-2-amine that was confirmed by LC/MS. ES/MS *m/z* 440(MH^+).

Example 33

Preparation of 4-(7-methoxy-4-methylquinazolin-2-ylamino)enzenesulfonamide (Compound 583)

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 1-(4-methoxy-2-aminophenyl)ethanone

To a 1:1 mixture of ethanol and acetic acid was added 1-(4-methoxy-2-nitrophenyl)ethanone (1eq) and Fe dust (3eq)was added in portions. The reduction was complete in 1h. The reaction mixture was filtered and then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and dried and concentrated to give methyl 1-(4-methoxy-2-aminophenyl)ethanone in 85 % yield. ES/MS *m/z* 196(MH^+).

Step 2. Preparation of 7-methoxy-4-methylquinazolin-2-ol

To methyl 1-(4-methoxy-2-aminophenyl)ethanone (1eq) was added urea (5eq) and few mls of acetic acid the mixture was heated to100°C for 16h. To the crude was added water and the precipitated solid was filtered to give methyl 7-methoxy-4-methylquinazolin-2-ol in quantitative yield. ES/MS *m/z* 191(MH^+).

Step 3. Preparation of 2-chloro-7-methoxy-4-methylquinazoline

To 7-methoxy-4-methylquinazolin-2-ol was added $POCl_3$ and the mixture was added heated to 100°C for 16h when the reaction went to completion. To the reaction mixture was added ice and

PP028218.0002

water and the precipitated solid was filtered and dried on the high vacuum overnight to give 2-chloro-7-methoxy-4-methylquinazoline in 60% yield. ES/MS *m/z* 209(MH^+).

Step 4. Preparation of 4-(7-methoxy-4-methylquinazolin-2-ylamino)benzenesulfonamide

To 2-chloro-7-methoxy-4-methylquinazoline(1eq) in isopropanol was added sulfanilide (1eq) and the mixture was heated to 90°C for 16h. The solid that precipitated was filtered and collected to give 4-(7-methoxy-4-methylquinazolin-2-ylamino)benzene sulfonamide. ES/MS *m/z* 345(MH^+).

Step 5. Preparation of 4-(7-hydroxy-4-methylquinazolin-2-ylamino)benzenesulfonamide

To 2-chloro-7-methoxy-4-methylquinazoline in NMP was added sodium thiomethoxide (4eq) and the mixture was added heated to 80°C for 16h when the reaction went to completion. To the reaction mixture was added water and ethyl acetate and ammonium chloride solution. The mixture was extracted with ethyl acetate and the organic layer was concentrated to give 4-(7-hydroxy-4-methylquinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 330(MH^+).

Step 6. Preparation of 4-(4-methyl-7-(2-(piperidin-4-yl)ethoxy)quinazolin-2-ylamino)benzene sulfonamide

To 4-(7-hydroxy-4-methylquinazolin-2-ylamino)benzenesulfonamide (1eq) in DMF was added potassium carbonate (1.1 eq) and KHMDS (1.2eq) and tert-butyl 4-(2-(methylsulfonyloxy)ethyl)piperidine-1-carboxylate (1.5eq). The reaction mixture was microwaved at 170°C for 10min. Formation of tert-butyl 4-(2-(4-methyl-2-(4-sulfamoylphenylamino)quinazolin-7-yloxy)ethyl)piperidine-1-carboxylate was confirmed by ^{1}HNMR and LC/MS.

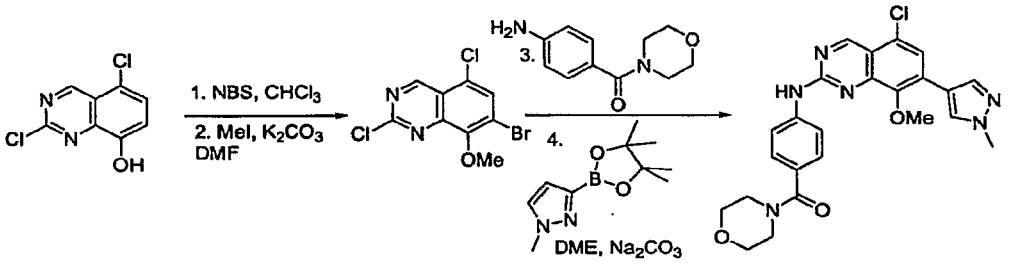
The crude reaction mixture of tert-butyl 4-(2-(4-methyl-2-(4-sulfamoylphenylamino) quinazolin-7-yloxy) ethyl) piperidine-1-carboxylate was purified using prep HPLC and the purified fractions of the product was concentrated. To it was added a few drops of 30% TFA/ DCM and the mixture was stirred for 30 min. The deprotection went to completion yielding 4-(4-methyl-7-(2-(piperidin-4-yl)ethoxy)quinazolin-2-ylamino)benzene sulfonamide that was confirmed by LC/MS. ES/MS *m/z* 442(MH^+).

PP028218.0002

Example 34

Preparation of (4-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)phenyl)(morpholino)methanone

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 7-bromo-2,5-dichloroquinazolin-8-ol

To 2,5-dichloroquinazolin-8-ol 91eq) in chloroform was added NBS (1eq) and the formation of 7-bromo-2,5-dichloroquinazolin-8-ol was instantaneous. The mixture was concentrated and confirmed by LC/MS. ES/MS *m/z* 294(MH^+).

Step 2. Preparation of 7-bromo-2,5-dichloro-8-methoxyquinazoline

To 7-bromo-2,5-dichloroquinazolin-8-ol (1eq) was added methyl iodide (1eq) and potassium carbonate (1eq) and the mixture was stirred for 16h at ambient temperature. Complete conversion to 7-bromo-2,5-dichloro-8-methoxyquinazoline was observed by HPLC. ES/MS *m/z* 308(MH^+).

Step 3. Preparation of (4-(7-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)phenyl) (morpholino)methanone

To 7-bromo-2,5-dichloro-8-methoxyquinazoline (1eq) was added (4-aminophenyl) (morpholino)methanone (1eq) in isopropanol and the mixture was heated to 90°C for 16h. The solid formed was filtered to give (4-(7-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)phenyl) (morpholino)methanone and was confirmed by LC/MS. ES/MS *m/z* 478(MH^+).

PP028218.0002

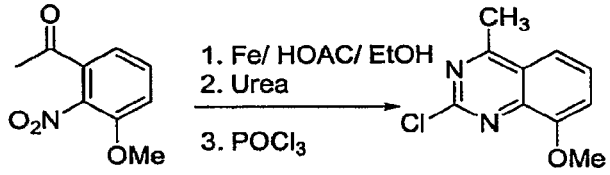
Step 4. Preparation pf N-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-yl)morpholine-4-carboxamide

To (4-(7-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)phenyl) (morpholino)methanone (1eq) in DME and 2M sodium carbonate solution was added 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was micro waved for 10 min at 120°C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was concentrated and purifiedon prep HPLC to yield N-(5-chloro-8-methoxy-7-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-yl)morpholine-4-carboxamide. ES/MS *m/z* 479(MH^+).

Example 35

Preparation of 2-chloro-8-methoxy-4-methylquinazoline

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 3-methoxy-2-aminobenzaldehyde

To a 1:1 mixture of ethanol and acetic acid was added 3-methoxy-2-nitrobenzaldehyde (1eq) and Fe dust (3eq)was added in portions. The reduction was complete in 3h. The reaction mixture was filtered and then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and dried and concentrated to give 2-amino-3-methoxybenzaldehyde in 85 % yield. ES/MS *m/z* 151(MH^+).

Step 2. Preparation of 8-methoxy-4-methylquinazolin-2-ol

To methyl 2-amino-3-methoxybenzaldehyde (1eq) was added urea (5eq) and few ml of acetic acid the mixture was heated to100°C for 16h. To the crude was added water and the precipitated solid was filtered to give methyl 8-methoxy-4-methylquinazolin-2-ol in quantitative yield. ES/MS *m/z* 191(MH^+).

PP028218.0002

Step 3. Preparation of 2-chloro-8-methoxy-4-methylquinazoline

To 8-methoxy-4-methylquinazolin-2-ol was added $POCl_3$ and the mixture was added heated to 100°C for 16h when the reaction went to completion. To the reaction mixture was added ice and water and the precipitated solid was filtered and dried on the high vacuum overnight to give 2-chloro-8-methoxy-4-methylquinazoline. ES/MS *m/z* 209(MH^+).

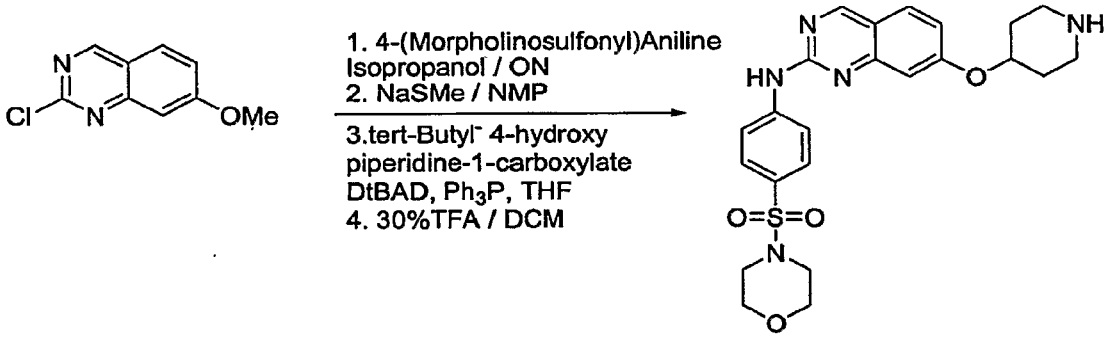
Example 36

Preparation of 4-(quinazolin-2-ylamino)benzenesulfonamide (Compound 618)

To 2-(4-sulfamoylphenylamino)quinazolin-6-yltrifluoromethane sulfonate in DMF was added $Pd(Ph_3)_2Cl_2$ (0.02eq) and formic acid (2eq) followed by tributylamine(3eq) and the mixture was heated to 110°C for 3h. Formation of the product was observed by LC/MS. The crude was purified on the prep to give 4-(quinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 301(MH^+).

Example 37

Synthesis of N- (4-(morpholinosulfonyl) phenyl-7- (piperidin-4-yloxy) quinazolin-2-amine (Compound 332)



Step 1. Preparation of 7-methoxy-N- (4-(morpholinosulfonyl) phenyl) quinazolin-2-amine

A mixture of 2-chloro-7-methoxyquinazoline (1eq) and 4-(Morpholinosulfonyl) Aniline (1eq) in 2-propanol was heated at 80°C overnight. Product was precipitated in the reaction mixture. The precipitate was filtered, washed and dried under vacuum to provide 7-methoxy-N- (4-

PP028218.0002

(morpholinosulfonyl) phenyl) quinazolin-2-amine as a yellow solid in 99% yield. ES/MS *m/z* 401.0(MH^+).

Step 2. Preparation of 2-(4-(morpholinosulfonyl)phenylamino)quinazolin-7-ol

A mixture of 7-methoxy-N- (4-(morpholinosulfonyl) phenyl) quinazolin-2-amine (1eq) and sodium thiomethoxide (4eq) in NMP was heated at 80°C for 4h. Reaction mixture was diluted with water and acidified with 1N HCl. Compound was extracted with ethyl acetate. The organic layer was washed with satd. $NaHCO_3$, brine and dried over sodium sulfate. Filtration, evaporation and drying under vacuum provide 2-(4-(morpholinosulfonyl) phenylamino) quinazolin-7-ol as a light yellow viscous liquid in 99% yield. ES/MS *m/z* 387.0(MH^+).

Step 3. Preparation of tert-butyl 4-(2-(4-(morpholinosulfonyl) phenylamino) quinazolin-7-yloxy) piperidine-1-carboxylate

To a solution of triphenylphosphine (2eq) in THF was added di-terbutylazodicarboxylate (2eq). The mixture was stirred 15 minutes at ambient temperature under nitrogen atmosphere. To that was added tert.butyl-4-hydroxypiperidine-1-carboxylate (5eq). The mixture was stirred 15 minutes at ambient temperature followed by addition of 2-(morpholinosulfonyl phenylamino) quinazolin-7-ol (1eq). The mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated and the residue was purified by flash column chromatography (50%EtOAc / Hexane) to provide product as a white solid in 80% yield. ES/MS *m/z* 570.1 (MH^+).

Step 4. N- (4-(morpholinosulfonyl) phenyl-7- (piperidin-4-yloxy) quinazolin-2-amine

A solution of tert-butyl 4-(2-(4-(morpholinosulfonyl) phenylamino) quinazolin-7-yloxy) piperidine-1-carboxylate in 30%TFA / DCM was stirred for 30min at ambient temperature. The solvent was evaporated and residue was purified by semi-prep HPLC to provide N- (4-(morpholinosulfonyl) phenyl-7- (piperidin-4-yloxy) quinazolin-2-amine in 80% yield. ES/MS *m/z* 470.1 (MH^+).

PP028218.0002

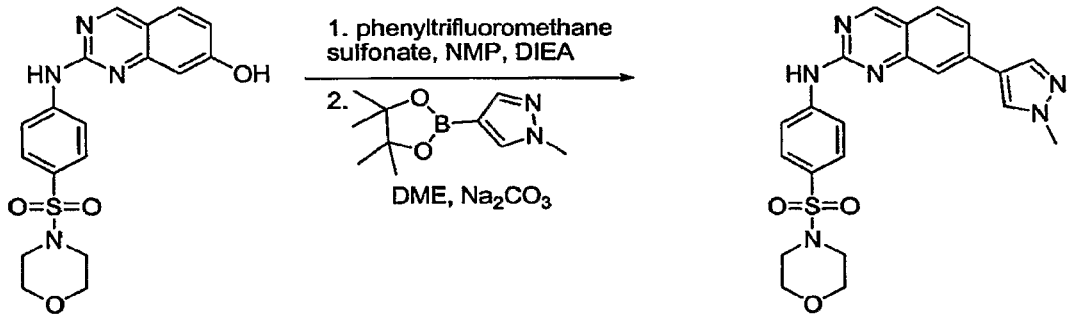
Example 38

Synthesis of 7-(1-(2-fluoroethyl) piperidine-4-yloxy)-N- (4-(morpholinosulfonyl) phenyl)quinazolin-2-amine (Compound 333)

To a solution of N- (4-(morpholinosulfonyl) phenyl-7- (piperidin-4-yloxy) quinazolin-2-amine (1eq) (See example 37, step 4) in DMF was added potassium carbonate (4eq) and 1-fluoro-2-iodoethane (1.2eq). The mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine. Dried over sodium sulfate, filtered, evaporated and purified by semi-preparative HPLC to provide 7-(1-(2-fluoroethyl) piperidine-4-yloxy)-N- (4-(morpholinosulfonyl) phenyl) quinazolin-2-amine as a yellow solid in 50% yield. ES/MS *m/z* 516.1 (MH^+).

Example 39

Synthesis of 7-(1-methyl-1H-pyrazol-4-yl) -N- (4-(morpholinosulfonyl) phenyl)quinazolin-2-amine (Compound 317)



Step 1. Preparation of 2-(4-(morpholinosulfonyl)phenylamino) quinazolin-7-yltrifluoromethane sulfonate

To a solution of 2-(4-(morpholinosulfonyl)phenylamino)quinazolin-7-ol (1eq) (See example 37, step 2) in NMP was added phenyltrifluoromethanesulfonate (1.2eq) and DIEA (2.5eq) and the reaction mixture was stirred over night at ambient temperature. The reaction mixture was then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium chloride, dried and concentrated. The crude was purified by flash chromatography (60%EtOAc / Hexane) to provide product as a white solid in 70% yield. ES/MS *m/z* 519.0(MH^+).

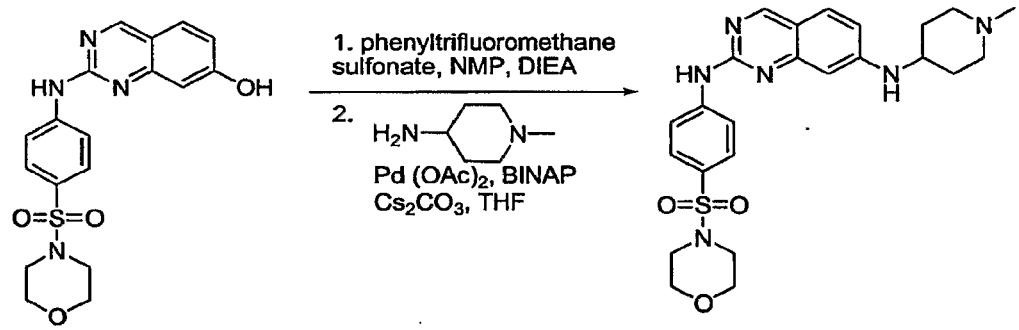
PP028218.0002

Step 2. Preparation of 7-(1-methyl-1H-pyrazol-4-yl) -N- (4-(morpholinosulfonyl) phenyl)quinazolin-2-amine

To a solution of 2-(4-(morpholinosulfonyl)phenylamino) quinazolin-7-yltrifluoromethane sulfonate (1eq) in DME was added 2M sodium carbonate solution and 1-methyl-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3eq) and Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was micro waved for 10 min at 120°C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated and purified by semi-preparative HPLC to provide 7-(1-methyl-1H-pyrazol-4-yl) -N- (4-(morpholinosulfonyl) phenyl) quinazolin-2-amine in 60%yield. ES/MS *m/z* 551.1(MH^+).

Example 40

Synthesis of N^7- (1-methylpiperidin-4-yl) –N^2- (4-(morpholinosulfonyl) phenyl) quinazolin-2, 7-diamine (Compound 348)



Step 1. Preparation of 2-(4-(morpholinosulfonyl)phenylamino) quinazolin-7-yltrifluoromethane sulfonate

For preparation see example 39 step 1.

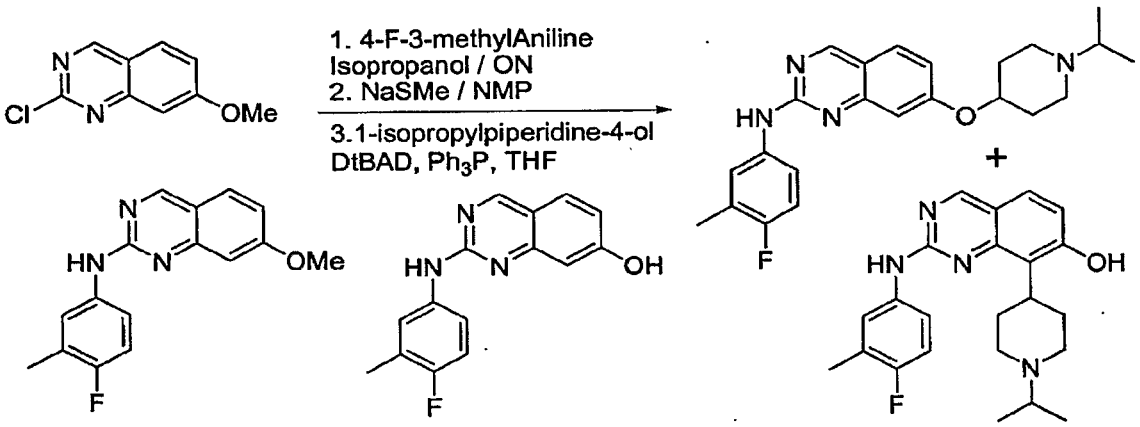
Step 2. Preparation of N^7- (1-methylpiperidin-4-yl) –N^2- (4-(morpholinosulfonyl) phenyl) quinazolin-2, 7-diamine

PP028218.0002

To a mixture of $Pd(OAc)_2$ (0.1eq), CS_2CO_3 (1.75eq) and BINAP (0.2eq) in THF was purged nitrogen for 10min. Then added to it was 2-(4-(morpholinosulfonyl)phenylamino) quinazolin-7-yltrifluoromethane sulfonate (1eq) and 4-amino-1-methylpiperidine (4eq). The reaction mixture was heated in sealed tube in oil bath for 3h at 110°C. The reaction mixture was concentrated and purified by semi-prep HPLC to provide N^7- (1-methylpiperidin-4-yl) $-N^2$- (4-(morpholinosulfonyl) phenyl) quinazolin-2, 7-diamine in 35% yield. ES/MS *m/z* 483.1 (MH^+).

Example 41

Synthesis of Preparation of N- (4-fluoro-3-methylphenyl)-7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-amine (Compound 327)



Step 1. Preparation of N- (4-fluoro-3-methylphenyl)-7-methoxy quinazolin-2-amine

See example 37, step 1 for synthesis. ES/MS *m/z* 284.0 (MH^+).

Step 2. Preparation of 2- (4-fluoro-3-methylphenylamino) quinazolin-7-ol

See example 37, step 2 for synthesis. ES/MS *m/z* 270.1 (MH^+).

Step 3. Preparation of N- (4-fluoro-3-methylphenyl)-7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-amine

To a solution of triphenylphosphine (2eq) in THF was added di-terbutylazodicarboxylate (2eq). The mixture was stirred 15 minutes at ambient temperature under nitrogen atmosphere. To that

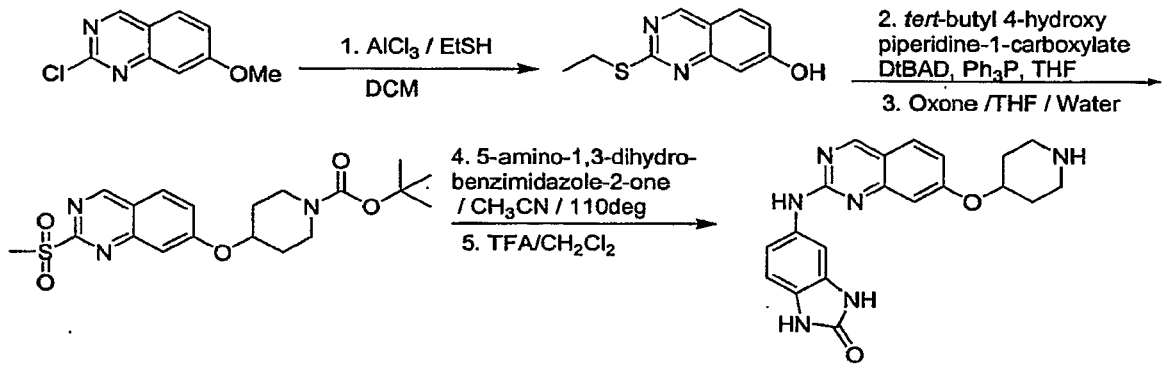
PP028218.0002

was added 1-isopropylpiperidine-4-ol (5eq). The mixture was stirred 15 minutes at ambient temperature followed by addition of 2-(4-fluoro-3-mrthylphenylamino) quinazolin-7-ol (1eq). The mixture was stirred overnight at ambient temperature. The LC –MS of reaction mixture shows the presence of two product (2:1) with identical mass. The reaction mixture was concentrated and purified by semi-preparative HPLC to provide (N- (4-fluoro-3-methylphenyl)-7-(1-isopropyl-piperidin-4-yloxy)-quinazolin-2-amine as a major product .ES/MS *m/z* 395.2 (MH^+).

The other product was identified by NMR as 2-(4-fluoro-3-methylphenylamino)-8-(1-isopropyl-piperidin-4-yl)-quinazolin-7-ol). ES/MS *m/z* 395.2 (MH^+).

Example 42

Synthesis of 5-(7-(piperidin-4-yloxy)-quinazolin-2-ylamino]- 1H-benzo[d] imidazol-2 (3H)-one (Compound 330)



Step 1. Preparation of 2-(ethylthio) quinazolin-7-ol

To a solution of ethanthiol (30ml) in DCM (50ml) was added $AlCl_3$ (6eq). The reaction mixture was cooled to 0°C and stirred for 10min under N_2 atmosphere. A solution of 2-chloro-7-methoxyquinazoline (1eq) in DCM (20ml) was added dropwise to it. The reaction mixture was warmed to room temperature and stirred for 2h. The solvent was evaporated and residue was partitioned between EtOAc and satd. NaHCO3. The insoluble material was filtered, washed and dried to provide title product as a yellow solid (yield, 60%). The ethyl acetate layer was separated from basic layer, washed with brine and dried over sodium sulfate. Filtration,

evaporation and drying under vacuum provide additional amount of product. (yield, 38%) . ES/MS *m/z* 207.0 (MH^+).

Step 2. Preparation of tert -butyl 4-(2-(ethylthio) quinazolin-7-yloxy) piperidine-1- carboxylate

To a solution of triphenylphosphine (2eq) in THF was added di-terbutylazodicarboxylate (2eq). The mixture was stirred 15 minutes at ambient temperature under nitrogen atmosphere. To that was added tert-butyl-4-hydroxypiperidine-1-carboxylate (5eq). The mixture was stirred 15 minutes at ambient temperature followed by addition of 2-(ethylthio) quinazolin-7-ol (1eq). The mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated and purified by flash column chromatography (10%EtOAc / Hexane) to provide product as a white solid in 90% yield. ES/MS *m/z* 390.1 (MH^+).

Step 3. Preparation of tert-butyl 4-(2-(ethylsulfonyl) quinazolin-7-yloxy) piperidine-1-carboxylate

To a solution of tert -butyl 4-(2-(ethylthio) quinazolin-7-yloxy) piperidine-1- carboxylate (1eq) in THF (5ml) was added a solution of oxone in water (5ml) at 0°C. The reaction mixture was stirred for 30min at 0°C then warmed to room temperature and stirred for 4h. The reaction was quenched with satd. sodium thiosulfate solution and basified with 1N NaOH. The product was extracted from basic layer with DCM. The DCM extracts were combined together, washed with brine and dried over sodium sulfate. The purification by flash column chromatography (70% EtOAc / Hexane) provide pure product in 60%yield. ES/MS *m/z* 422.0 (MH^+).

Step 4. Preparation of tert-butyl 4-(2-(2-oxo-2, 3-dihydro-1H-benzo[d]imidazol-5-ylamino) quinazolin-7-yloxy) piperidine-1- carboxylate

A solution of tert-butyl 4-(2-(ethylsulfonyl) quinazolin-7-yloxy) piperidine-1- carboxylate (1eq) and 5-amino-1, 3-dihydro-benzimidazole-2-one (5eq) in acetonitrile was heated in sealed tube at 110°C for 48h. The product was filtered, washed and dried. A brown solid, yield 50%. ES/MS *m/z* 477.5 (MH^+).

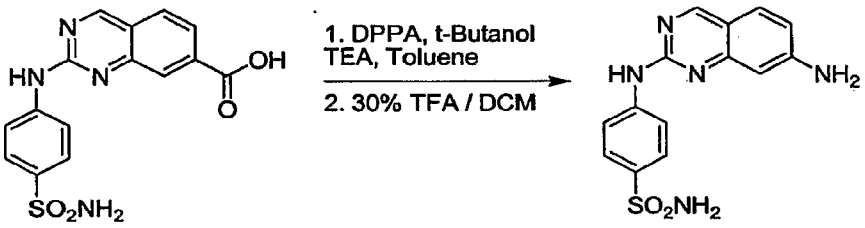
Step 5. Preparation of 5-(7-(piperidin-4-yloxy)-quinazolin-2-ylamino]- 1H-benzo[d]imidazol-2(3H)-one

PP028218.0002

A solution of crude tert-butyl 4-(2-(2-oxo-2, 3-dihydro-1H-benzo[d]imidazol-5-ylamino) quinazolin-7-yloxy) piperidine-1- carboxylate in 30%TFA / DCM was stirred at room temperature for 30min. The solvent was evaporated and crude was purified by semi-prep HPLC to provide pure product in 30% yield. ES/MS *m/z* 377.1 (MH^+).

Example 43

Synthesis of 4-(7-aminoquinazolin-2-ylamino]- benzenesulfonamide (Compound 315)



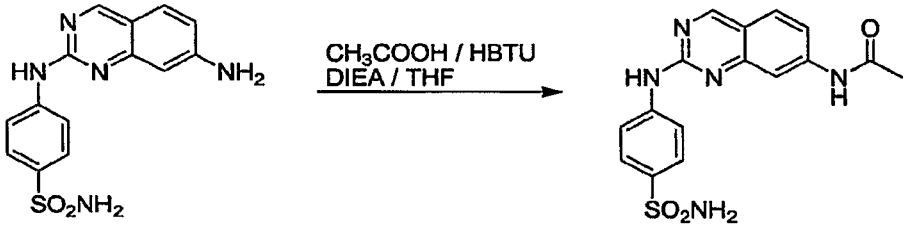
Step 1. Preparation of tert-butyl 2-(4-sulfamoylphenylamino) quinazolin-7-yl) carbamate
To 2-(4-sulfamoylphenylamino) quinazoline-7-carboxylic acid (1eq) in toluene was added diphenylphosphorylazide (1.2eq), tert-butanol (10eq) and triethylamine (2eq). The reaction mixture was heated at 70°C for 30min then 100°C for overnight. The reaction mixture was concentrated and purified by semi-prep HPLC to provide pure product as a yellow solid in 35% yield. ES/MS *m/z* 416.0` (MH^+).

Step 2. Preparation of 4-(7-aminoquinazolin-2-ylamino]- benzenesulfonamide
A solution of tert-butyl 2-(4-sulfamoylphenylamino) quinazolin-7-ylcarbamate in 30%TFA / DCM was stirred at room temperature for 30min. The solvent was evaporated and crude was purified by semi-prep HPLC to provide 4-(7-aminoquinazolin-2-ylamino]-benzenesulfonamide. ES/MS *m/z* 316.0 (MH^+).

Example 45

Synthesis of N- (2-(4- sulfamoylphenylamino) quinazolin-7-yl) acetamide (Compound 316)

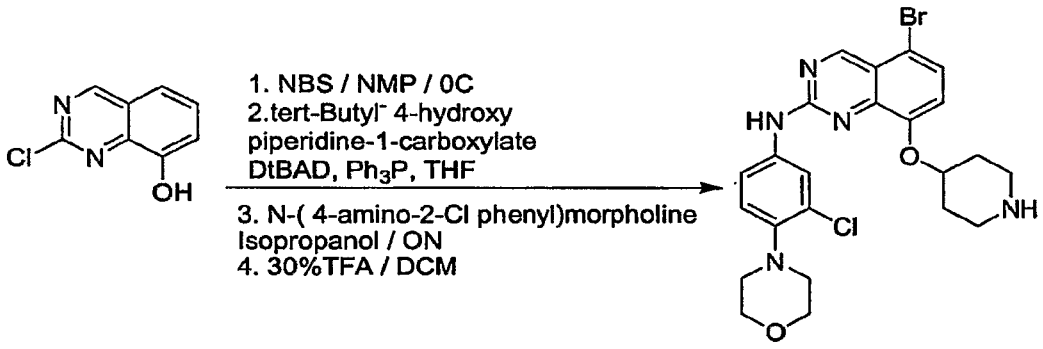
PP028218.0002



To a solution of 4-(7-aminoquinazolin-2-ylamino]- benzenesulfonamide (1eq) (For synthesis see example 43) in THF was added acetic acid (5eq), HBTU (4eq) and DIEA (10eq). The reaction mixture was stirred at room temperature for 48h. The reaction does not go to completion. Diluted with ethyl acetate and washed with water, brine and dried over sodium sulfate. Filtered, concentrated and purified by semi-prep HPLC to provide N- (2-(4- sulfamoylphenylamino) quinazolin-7-yl) acetamide ES/MS *m/z* 358.0 (MH^+).

Example 45

Synthesis 5-bromo-N- (3- chloro-4-morpholinophenyl)-8-(piperidine-4-yloxy) quinazolin-2-amine (Compound 338)



Step 1. Preparation of 5-bromo-2-chloroquinazolin-8-ol

Solid NBS (1eq) was added to a stirred solution of 2-chloroquinazolin-8-ol (1eq) (See example 1 for synthesis) in NMP at 0°C under argon. After stirring at 0°C for 30min, LCMS showed that the reaction was complete. The formation of both 5-bromo (Major) and 7-bromo (Minor) isomers

along with 5,7 dibromo product was observed. The reaction mixture was diluted with ethyl acetate and washed with satd. sodium bicarbonate, water and brine. Dried, filtered and concentrated. The crude was purified by flash chromatography (3-5% EtOAc / Hexane) to provide 5-bromo-2-chloroquinazolin-8-ol as a white solid in 60% yield. ES/MS *m/z* 259.2 (MH^+).

Step 2. Preparation of tert-butyl 4-(5-bromo-2-chloroquinazolin-8-yloxy) piperidine-1-carboxylate

To a solution of triphenylphosphine (2eq) in THF was added di-terbutylazodicarboxylate (2eq). The mixture was stirred 15 minutes at ambient temperature under nitrogen atmosphere. To that was added tert.butyl-4-hydroxypiperidine-1-carboxylate (5eq). The mixture was stirred 15 minutes at ambient temperature followed by addition of 5-bromo-2-chloroquinazolin-8-ol (1eq). The mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated and the residue was purified by flash column chromatography (25%EtOAc / Hexane) to provide product as a white solid in 90% yield. ES/MS *m/z* 442.1 (MH^+).

Step 3. Preparation of tert-butyl 4-(5-bromo-2-(3-chloro-4-morpholinophenylamino) quinazolin-8-yloxy) piperidine-1-carboxylate

A mixture of tert-butyl 4-(5-bromo-2-chloroquinazolin-8-yloxy) piperidine-1-carboxylate (1eq) and N- (4-amino-2-chlorophenyl) morpholine (1eq) in isopropanol was heated in a sealed tube at 110°C for overnight. The reaction mixture was concentrated and proceeds for next step. ES/MS *m/z* 618.0 (MH^+).

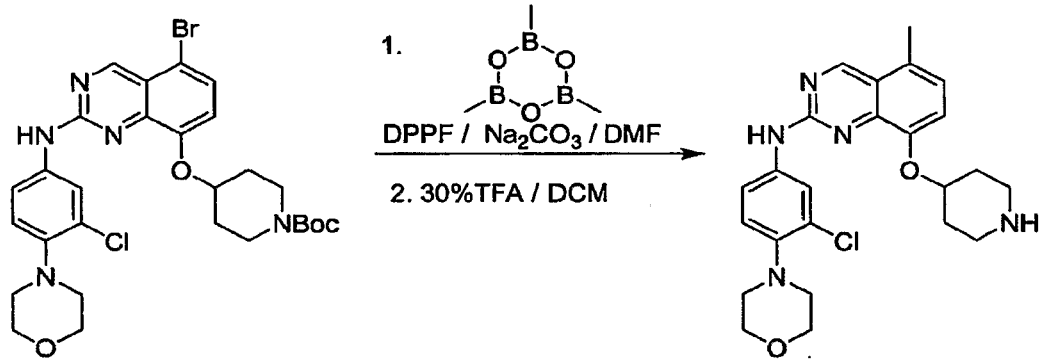
Step 4. Preparation of 5-bromo-N- (3- chloro-4-morpholinophenyl)-8-(piperidine-4-yloxy) quinazolin-2-amine

A solution of tert-butyl 4-(5-bromo-2-(3-chloro-4-morpholinophenylamino) quinazolin-8-yloxy) piperidine-1-carboxylate in 30%TFA / DCM was stirred at room temperature for 30min. The solvent was evaporated and crude was purified by semi-prep HPLC to provide 5-bromo-N- (3-chloro-4-morpholinophenyl)-8-(piperidine-4-yloxy) quinazolin-2-amine in 50% yield. ES/MS *m/z* 518.0 (MH^+).

PP028218.0002

Example 46

Synthesis of N-(3-chloro-4-morpholinophenyl)-5-methyl-8- (piperidine-4-yloxy) quinazolin-2-amine (Compound 602)



Step 1. Preparation of tert-butyl 4-(2- (3-chloro-4-morpholinophenylamino)-5-methylquinazolin-8-yloxy) piperidine-1-carboxylate

To a solution of tert-butyl 4-(5-bromo-2- (3-chloro-4-morpholinophenylamino) quinazolin-8-yloxy) piperidine-1-carboxylate (See example 45 for synthesis) (1eq) in DMF was added 2M sodium carbonate solution, trimethylboroxine (3eq) and Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq). The reaction mixture was micro waved for 10 min at 120°C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated and purified by semi-preparative HPLC to provide pure product . ES/MS *m/z* 554.1(MH^+).

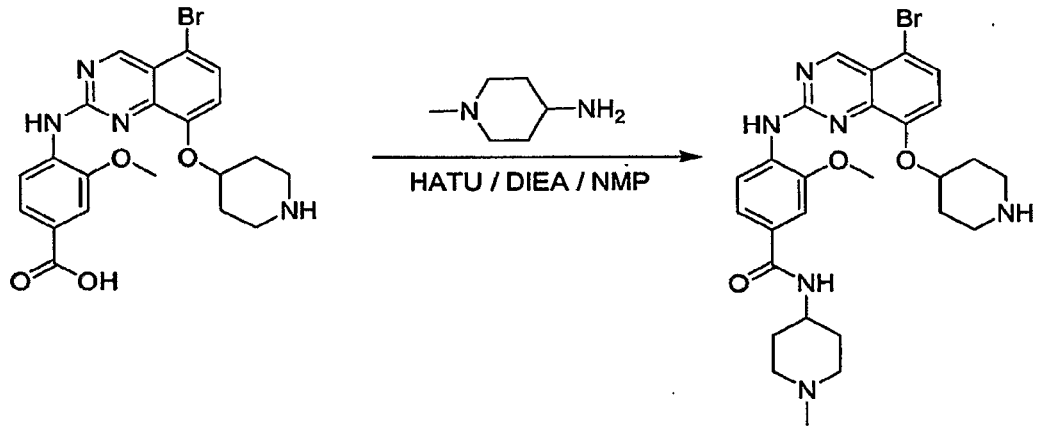
Step 2. Preparation of N- (3- chloro-4-morpholinophenyl)-5-methyl-8- (piperidine-4-yloxy) quinazolin-2-amine

A solution of tert-butyl 4-(2- (3-chloro-4-morpholinophenylamino)-5-methylquinazolin-8-yloxy) piperidine-1-carboxylate in 30%TFA / DCM was stirred at room temperature for 30min. The solvent was evaporated and crude was purified by semi-prep HPLC to provide N- (3- chloro-4-morpholinophenyl)-5-methyl-8- (piperidine-4-yloxy) quinazolin-2-amine 50% yield. ES/MS *m/z* 454.1 (MH^+).

PP028218.0002

Example 47

Synthesis of 4-(5-bromo-8- (piperidin-4-yloxy) quinazolin-2-ylamino)-3-methoxy-N- (1-methylpiperidinyl)benzamide (Compound 371)



For preparation of the starting material, 4-(5-bromo-8- (piperidine-4-yloxy)quinazolin-2-ylamino)-3-methoxybenzoic acid see example 45. ES/MS *m/z* 473.0 (MH^+).

Preparation of 4-(5-bromo-8- (piperidin-4-yloxy)quinazolin-2-ylamino)-3-methoxy-N-(1-methylpiperidinyl)benzamide

A mixture of 4-(5-bromo-8-(piperidine-4-yloxy)quinazolin-2-ylamino)-3-methoxybenzoic acid (1eq), 4-amino-N-methylpiperidine (2eq), HATU (1.5eq) and DIEA (3eq) in NMP was stirred at room temperature for 4h. The reaction mixture was concentrated and purified by semi-prep HPLC to provide pure product in 45% yield.

ES/MS *m/z* 569.1 (MH^+).

Example 48

Synthesis (2-chloro-4- (5-chloro-8- (piperidin-4-yloxy) quinazolin-2-ylamino)phenyl) (morpholino)methanone (Compound 692)

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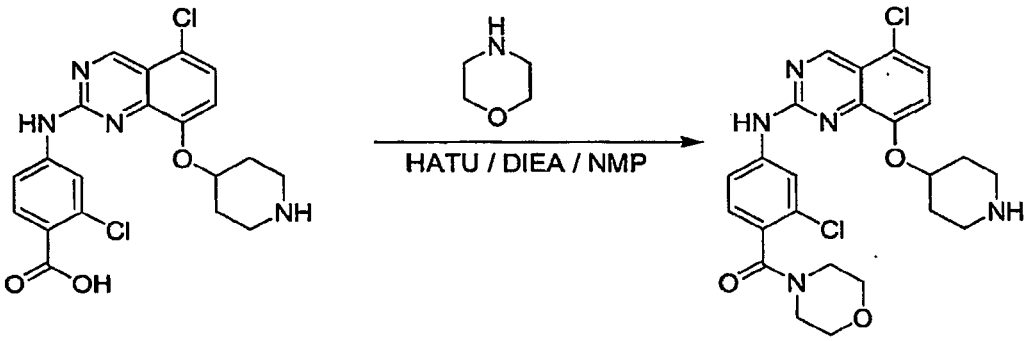


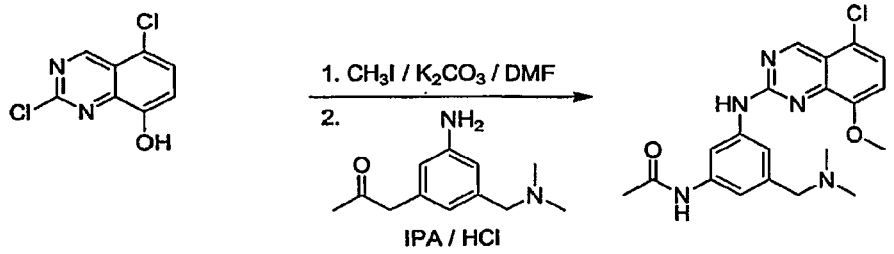
For preparation of the starting material, 2-chloro-4- (5-chloro-8- (piperidin-4-yloxy) quinazolin-2-ylamino) benzoic acid, see example 32 for the synthesis. ES/MS *m/z* 433.0 (MH^+).

Preparation of (2-chloro-4- (5-chloro-8- (piperidin-4-yloxy) quinazolin-2-ylamino)phenyl) (morpholino)methanone

A mixture of 2-chloro-4- (5-chloro-8- (piperidin-4-yloxy) quinazolin-2-ylamino) benzoic acid (1eq), morpholine (3eq), HATU (1.5eq) and DIEA (4eq) in NMP was stirred at room temperature for 4h. The reaction mixture was concentrated and purified by semi-prep HPLC to provide pure product in 50% yield. ES/MS *m/z* 502.3 (MH^+).

Example 49

Synthesis N- (3-chloro-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)methyl) phenyl)acetamide (Compound 691)



Step 1. Preparation of 2,5 –dichloro-8-methoxyquinazoline

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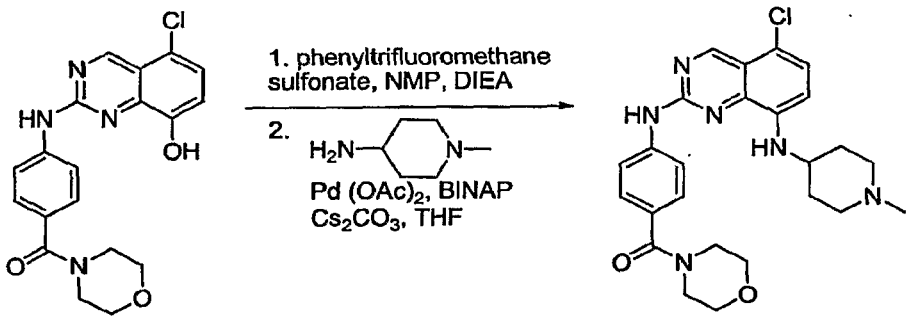
To a solution of 2,5-dichloroquinazolin-8-ol (1eq) (See example 32 for synthesis) in DMF was added iodomethane (3eq) and potassium carbonate (3eq). The reaction mixture was stirred at room temperature for overnight. Diluted with ethyl acetate and washed with water and brine and dried over sodium sulfate. Filtered, evaporated and dried to provide product as a yellow solid in quantitative yield. ES/MS *m/z* 229.0 (MH^+). Proceed for next step.

Step 2. Preparation of (3-chloro-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino) methyl) phenyl) acetamide

A mixture of 2,5 –dichloro-8-methoxyquinazoline (1eq) and 1-(3-amino-5-((dimethylamino)methyl)phenyl)propan-2-one (1eq) and 6NHCl (1.1eq) in isopropanol was heated at 120°C for overnight. The reaction mixture was concentrated and purified by semi-prep HPLC to provide pure product in 30% yield. ES/MS *m/z* 400.2 (MH^+).

Example 50

Synthesis (4-(5-chloro-8- (1-methylpiperidin-4-ylamino) quinazolin-2-ylamino)phenyl) (morpholino)methanone (Compound 377)



Step 1. Preparation of (4-(5-chloro-8-hydroxyquinazolin-2-ylamino) phenyl) (morpholino)methanone

See example 32 for synthesis. ES/MS *m/z* 385.0(MH^+).

PP028218.0002

Step 2. Preparation of 5-chloro-2- (4-(morpholino-4-carbonyl) phenylamino) quinazolin-8-yltrifluoromethane sulfonate

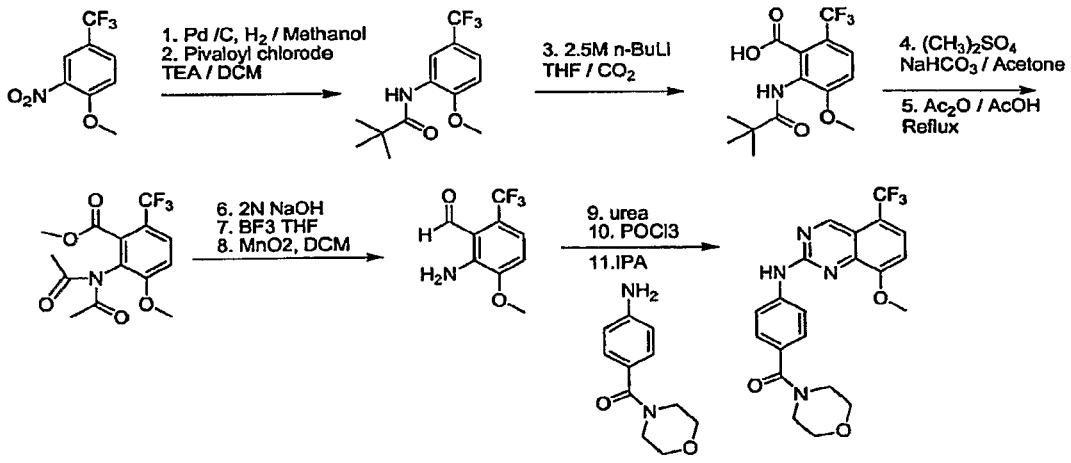
See example 39, step1 for synthesis. ES/MS *m/z* 517.0(MH^+).

Step 3. Preparation of (4-(5-chloro-8- (1-methylpiperidin-4-ylamino) quinazolin-2-ylamino)phenyl)(morpholino)methanone

To a mixture of Pd $(OAc)_2$ (0.1eq), CS_2CO_3 (1.75eq) and BINAP (0.2eq) in THF was purged nitrogen for 10min. Then added to it were 5-chloro-2- (4-(morpholino-4-carbonyl) phenylamino) quinazolin-8-yltrifluoromethane sulfonate (1eq) and 4-amino-1-methylpiperidine (2eq). The reaction mixture was heated in sealed tube in oil bath for 16h at110°C. The reaction mixture was concentrated and purified by semi-prep HPLC to provide (4-(5-chloro-8- (1-methylpiperidin-4-ylamino) quinazolin-2-ylamino) phenyl) (morpholino)methanone in 35% yield. ES/MS *m/z* 481.0 (MH^+).

Example 51

Synthesis of 4-(8-methoxy-5- (trifluoromethyl) quinazolin-2-ylamino) phenyl)(morpholino)methanone (Compound 500)



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Step 1. Preparation of 2-methoxy-5- (trifluoromethyl) aniline
A mixture of 4-methoxy-3-nitrobezotrifluoride and 10% of 10% Pd / C in methanol was stirred under H_2 atmosphere overnight at room temperature. The reaction mixture was filtered through celite, concentrated and dried under vacuum to provide product as an off white solid in 99%yield. ES/MS *m/z* 192.1 (MH^+).

Step 2. Preparation of N- (2-methoxy-5-(trifluoromethyl) phenyl) pivalamide
To a solution of 2-methoxy-5- (trifluoromethyl) aniline (1eq) in DCM at 0 °C was added TEA (1eq) followed by dropwise addition of pivaloyl chloride (1eq). The reaction mixture was warmed to room temperature and left stirred overnight. Diluted with DCM and washed with satd. sodium bicarbonate, water, brine and dried over sodium sulfate. Filtered, evaporated and dried under vacuum to provide pure product as an off white solid in 95% yield. ES/MS *m/z* 276.1 (MH^+).

Step 3. Preparation of 3-methoxy-2-pivalamido-6- (trifluoromethyl) benzoic acid
N- (2-methoxy-5- (trifluoromethyl) phenyl) pivalamide (1eq) was azeotrope with toluene (x=3). Dissolved in THF, cooled to -50 °C and added n-BuLi (2eq, 2.5M solution in hexane) dropwise. The reaction mixture was stirred at -50 °C for 1h then warmed to -10 °C in 30min. Stirred at this temperature for 30min then CO_2 gas was passed through cylinder into the reaction mixture at -10 to 0°C for 1h. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was poured to water and extracted with ethyl acetate. (EtOAc extracts contained starting material). The aq layer pH was adjusted to 1-2 and product was extracted with ethyl acetate (x=3). The ethyl acetate extracts were combined, washed with brine and dried over sodium sulfate.
Filtered, evaporated and dried under vacuum to provide product as yellow solid in 65% yield. ES/MS *m/z* 320.1 (MH^+). Proceeds for next step without any purification.

Step 4. Preparation of methyl-3-methoxy-2-pivalamido-6-(trifluoromethyl) benzoate
A mixture of 3-methoxy-2-pivalamido-6- (trifluoromethyl) benzoic acid (1eq), dimethyl sulfate (1eq) and sodium bicarbonate (1.3eq) in acetone was refluxed for 4h. The reaction mixture was poured to water and extracted with ethyl acetate. The ethyl acetate extracts were combined,

washed with brine and dried over sodium sulfate. Filtered, evaporated and dried under vacuum to provide product as yellow solid in 95% yield. ES/MS *m/z* 334.1 (MH^+). Proceeds for next step without any purification.

Step 5. Preparation of methyl-2- (acetylacetamido)-3-methoxy-6-(trifluoromethyl) benzoate
A solution of methyl-3-methoxy-2-pivalamido-6- (trifluoromethyl) benzoate in acetic acid and acetic anhydride (1:2) was heated to reflux for 16h. The reaction mixture was concentrated and residue was partitioned between ether and water. Ether layer was separated and washed with water, satd.sodium bicarbonate and dried over sodium sulfate.
Filtered, evaporated and dried. The residue was triturated with hexane and solid was collected by filtration and dried under vacuum to provide pure product as an off white solid in 60% yield. ES/MS *m/z* 334.1 (MH^+).

Step 6. Preparation of 2-amino -3-methoxy-6- (trifluoromethyl) benzoic acid
A solution of methyl-2- (acetylacetamido)-3-methoxy-6-(trifluoromethyl) benzoate in 2N NaOH was heated to reflux for 4-5h. The reaction mixture was cooled and pH was adjusted to 2. The product was extracted in ethyl acetate. The ethyl acetate extracts were combined, washed with brine and dried over sodium sulfate. Filtered, evaporated and residue was triturated with hexane. The solid was collected by filtration and dried under vacuum to provide product as light brown solid in 85% yield. ES/MS *m/z* 236.0 (MH^+).

Step 7. Preparation of 2-amino -3-methoxy-6- (trifluoromethyl) phenyl) methanol
To 2-amino -3-methoxy-6- (trifluoromethyl) benzoic acid (1eq) in THF at 0°C was added boran tetrahydrofuran complex solution (6eq, 1 M in THF) at different time interval. The mixture was stirred at room temperature for 48 hrs. The solvent was removed in vacuo and residue was partitioned between water and ethyl acetate.The organic layer was separated, washed with brine, dried with sodium sulfate and concentrated to give product in 85% yield. ES/MS *m/z* 222.1 (MH^+).

PP028218.0002

Step 8. Preparation of 2-amino -3-methoxy-6- (trifluoromethyl) benzaldehyde

To 2-amino -3-methoxy-6- (trifluoromethyl) phenyl) methanol (1eq) in dichloromethane was added manganese dioxide (5eq). The mixture was stirred at room temperature under argon for 48 hrs. The mixture was filtered through celite pad and washed thoroughly with dichloromethane. The filtrated was concentrated in vacuo to give crude product in 90% yield, which was used for the next step without further purification. ES/MS *m/z* 220.0 (MH^+).

Step 9. Preparation of 8-methoxy-5-(trifluoromethyl) quinazolin-2-ol

A mixture of 2-amino -3-methoxy-6- (trifluoromethyl) benzaldehyde (1eq) (obtained from step 7) and urea (15 equiv.) was heated to 175 °C with vigorous stirring for 2h. The reaction was cooled to room temperature and water was added. The solid was collected by filtration. Air-dried to give 8-methoxy-5- (trifluoromethyl) quinazolin-2-ol as yellow solid in 70%yield. ES/MS *m/z* 245.0 (MH^+).

Step 10. Preparation of 2-chloro-8-methoxy-5- (trifluoromethyl) quinazoline

The crude 8-methoxy-5-(trifluoromethyl) quinazolin-2-ol was heated in neat phosphooxychloride ($POCl_3$) at 110 °C for 2h. The resulted mixture was cooled to room temperature and concentrated in vacuo to nearly dryness. Ice water was added and precipitate was filtered, washed and dried to provide 2-chloro-8-methoxy-5- (trifluoromethyl) quinazoline as a light pink solid in 70% yield. ES/MS *m/z* 263.0 (MH^+).

Step 11. Preparation of 4-(8-methoxy-5- (trifluoromethyl) quinazolin-2-ylamino) phenyl)(morpholino)methanone

A mixture of 2-chloro-8-methoxy-5- (trifluoromethyl) quinazoline (1eq) and 4-amino phenyl)(morpholino)methanone (1eq) in isopropanol was heated in sealed tube at 110 °C for 16h. The solvent was evaporated and residue was purified by semi-prep HPLC to provide pure product as yellow solid in 50% yield. ES/MS *m/z* 433.2 (MH^+).

Example 52

Synthesis of morpholino(4-(8-piperidin-4-yloxy)-5-(trifluoromethyl) quinazolin-2-ylamino) phenyl) methanone (Compound 383)

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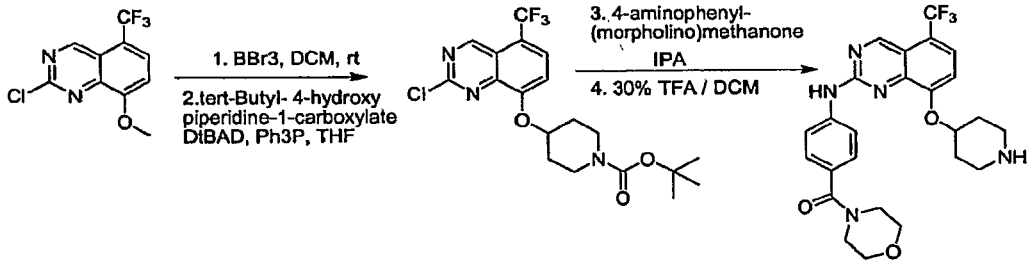


Step 1. Preparation of 2-chloro-5- (trifluoromethyl) quinazolin-8-ol

To a solution of 2-chloro-8-methoxy-5- (trifluoromethyl) quinazoline (1eq) (See example 51 for synthesis) in DCM was added boron tribromide at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated and residue was treated with ice cold water. Precipitate was filtered, washed and dried in vacuo to provide product as a yellow solid in 78% yield. ES/MS *m/z* 249.0 (MH^+).

Step 2. Preparation of tert.butyl-4- (2-chloro-5- (trifluoromethyl) quinazolin-8-yloxy) piperidine-1-carboxylate

See example 37, step 2 for the synthesis. ES/MS *m/z* 431.2 (MH^+).

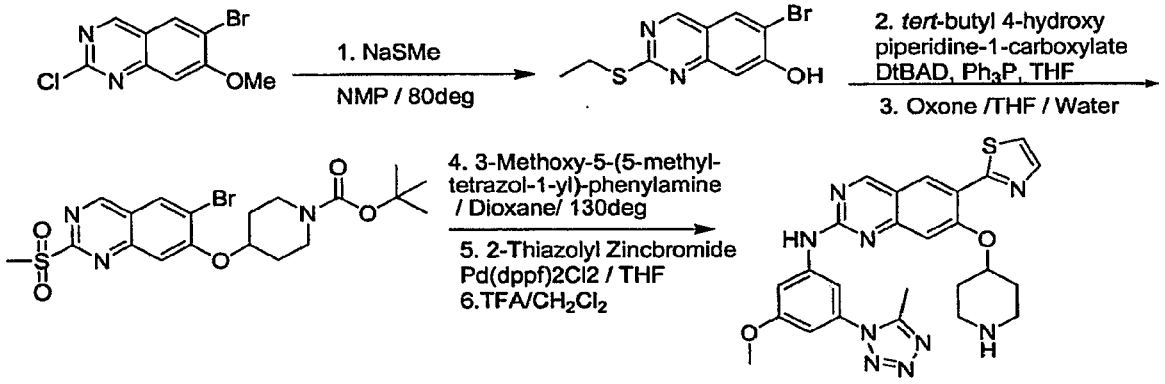
Step 3 - 4. Preparation of morpholino(4-(8-piperidin-4-yloxy)-5-(trifluoromethyl) quinazolin-2-ylamino) phenyl) methanone

See example 45, step 3 and 4 for the synthesis. ES/MS *m/z* 502.2 (MH^+).

Example 53

Synthesis of N- (3-methoxy-5 (5-methyl-1H-tetrazol-1-yl)phenyl)-7 –(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine (Compound 682)

PP028218.0002



Step 1. Preparation of 6-bromo-2-(ethylthio) quinazolin-7-ol

For preparation, see example 37, step 2. (yield, 60%). ES/MS *m/z* 270.9 (MH^+).

Step 2. Preparation of tert -butyl 4-(6-bromo-2- (methylsulfonyl) quinazolin-7-yloxy) piperidine-1- carboxylate

Step 2 &3. See example 42, step 2 and 3 for the synthesis. (yield, 70%) ES/MS *m/z* 454 / 456 (MH^+).

Step 4. Preparation of tert -butyl 4-(6-bromo-2- (3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenylamino)) quinazolin-7-yloxy) piperidine-1- carboxylate

A mixture of tert -butyl 4-(6-bromo-2- (methylsulfonyl) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq) and 3-Methoxy-5- (5-methyl-tetrazol-1-yl)-phenylamine (2eq) in dioxane was heated in sealed tube at 120°C for 48h. The product was purified by semi prep HPLC to provide pure product as a brown solid. ES/MS *m/z* 611.0 / 613.0 (MH^+).

Step 5 & 6. Preparation of N- (3-methoxy-5- (5-methyl-1H-tetrazol-1-yl) phenyl)-7-(piperidin-4-yloxy) –6-(thiazol-2-yl) quinazolin-2-amine

See example 27 for the synthesis. ES/MS *m/z* 516.1 (MH^+).

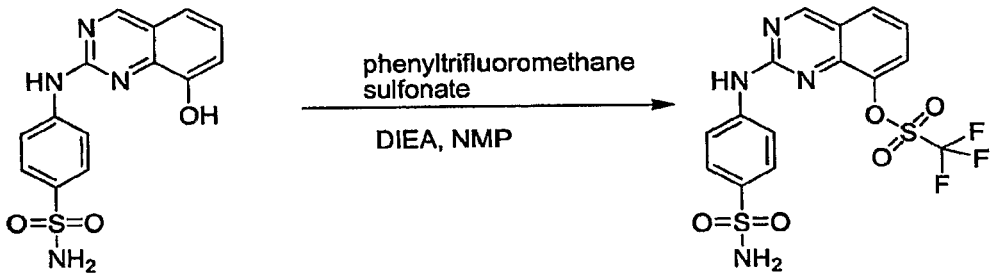
PP028218.0002

Example 54

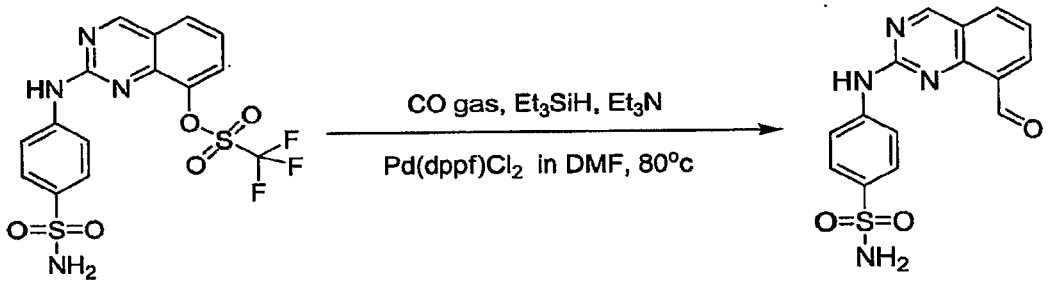
Preparation of 4-(8-(((2-methoxyethyl)(methyl)amino)methyl)quinazolin-2-ylamino)benzenesulfonamide (Compound 392)

The subject compound was prepared according to the general Scheme below:

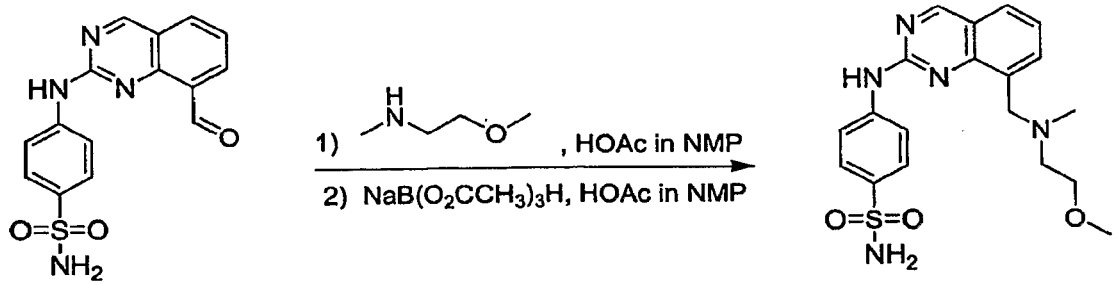
Step 1



Step2



Step3



Step 1. Preparation of 2-(4-sulfamoylphenylamino)quinazolin-8-yl-trifluoromethanesulfonate To a solution of 4-(8-hydroxyquinazolin-2-ylamino) benzenesulfonamide in NMP was added phenyltrifluoromethanesulfonate and DIEA and the reaction mixture was stirred over night at ambient temperature. The reaction mixture was then partitioned between ethyl acetate and

water. The organic layers were washed with saturated sodium chloride and dried and concentrated. To the crude was added methylene chloride and few drops of methanol. The white solid hence formed was filtered to give 2-(4-sulfamoylphenylamino)quinazolin-8-yltrifluoromethane sulfonate.

Step 2. Preparation of 4-(8-formylquinazolin-2-ylamino)benzenesulfonamide
A mixture of 2-(4-sulfamoylphenylamino)quinazolin-8-yl trifluoromethanesulfonate (900 mg, 2 mmole), $Pd(dppf)Cl_2$ (170 mg, 0.2 mmole), triethylamine (700 ul, 5 mmole) and triethylsilane (960 ul, 6 mmole) in DMF (20 ml) was placed in a stainless steel reactor. CO was bubbled into the mixture in the reactor. The reaction solution was stirred at 85°c under CO (420 psi) for overnight. The reaction mixture was poured into 80 ml of saturated $NaHCO_3$ and extracted with ethyl acetate (2x250 ml). The combined organic layers were washed with water (2x60 ml) and brine (60 ml), then dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography to give 4-(8-formylquinazolin-2-ylamino)benzenesulfonamide (274 mg, 0.83 mmole) as brown solid. ES/MS *m/z* 328.9(MH^+).

Step 3, Preparation of 4-(8-(((2-methoxyethyl)(methyl)amino)methyl)quinazolin-2-ylamino)benzenesulfonamide
To the solution of 4-(8-formylquinazolin-2-ylamino)benzenesulfonamide (11 mg, 30 umole) and 2-methoxy-N-methylethanamine (37 ul, 30 umole) in 500 ul of NMP was added a few drops of acetic acid. The reaction solution was stirred at room temperature for overnight. Sodium triacetoxy borohydride (7 mg, 33 umole) was added. The reaction mixture was stirred for 2hr at ambient temperature. The reductive amination went to completion to give 4-(8-(((2-methoxyethyl)(methyl)amino)methyl)quinazolin-2-ylamino)benzenesulfonamide that was then purified on prep HPLC to give product as powder . ES/MS *m/z* 402.2 (MH^+).

Example 55

Preparation of 4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)-5-(trifluoromethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme below:

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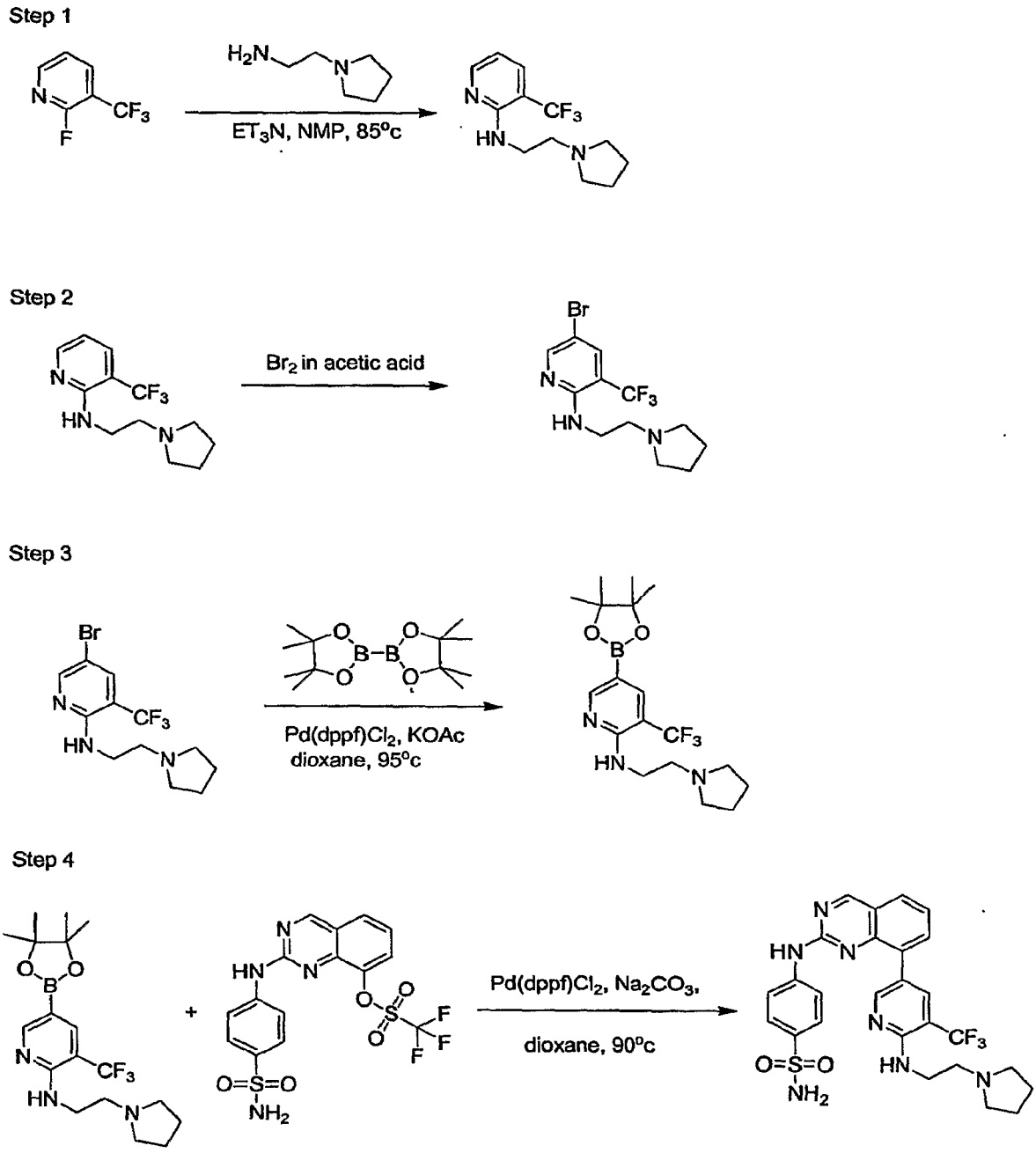


Step1. Preparation of N-(2-(pyrrolidin-1-yl)ethyl)-3-(trifluoromethyl)pyridin-2-amine

To the solution of 2-fluoro-3-(trifluoromethyl)pyridine (990 mg, 6 mmole) in 5 ml of NMP, 2-aminoethylpyrrolidine (1.13 ml, 9 mmole) and triethylamine (1 ml, 7.2 mmole) were added. The

PP028218.0002

reaction solution was stirred at 85°c for overnight. The reaction mixture was poured into 40 ml of saturated $NaHCO_3$ and extracted with ethyl acetate (2x80 ml). The combined organic layers were washed with water (2x30 ml) and brine (30 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown oily N-(2-(pyrrolidin-1-yl)ethyl)-3-(trifluoromethyl)pyridin-2-amine (1.61g). ES/MS *m/z* 260.1 (MH^+).

Step 2. Preparation of 5-bromo-N-(2-(pyrrolidin-1-yl)ethyl)-3-(trifluoromethyl)pyridin-2-amine. To the solution of N-(2-(pyrrolidin-1-yl)ethyl)-3-(trifluoromethyl)pyridin-2-amine (1030 mg, 4 mmole) in 10 ml of acetic acid, bromine (203 ul, 4 mmole) was added. The reaction solution was stirred at room temperature for 1.5 hr and then concentrated under vacuo to give an orange solid. The crude product was dissolved with 40 ml of ethyl acetate to give a yellow milky mixture that was then filtered and washed to give an invory powder as HBr salt of 5-bromo-N-(2-(pyrrolidin-1-yl)ethyl)-3-(trifluoromethyl)pyridin-2-amine (963 mg). ES/MS *m/z* 335.9, 337.9 (MH^+).

Step 3. Preparation of N-(2-(pyrrolidin-1-yl)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine.
A mixture of 5-bromo-N-(2-(pyrrolidin-1-yl)ethyl)-3-(trifluoromethyl)pyridin-2-amine as TFA salt (356 mg, 789 umole), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (219 mg, 862 umole) and potassium acetate (231 mg, 2.35 mmole) in 4 ml of dioxane, $Pd(dppf)Cl_2$ (41 mg, 50 umole) was added into the reaction mixture that was stirred at 92°c for overnight. The reaction mixture was saved for future reaction and analyzed by LCMS to characterize the product as N-(2-(pyrrolidin-1-yl)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine.

Step 4. Preparation of 4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)-5-(trifluoromethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide.
To the reaction mixture of N-(2-(pyrrolidin-1-yl)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (1.2 ml, 235 umole) in dioxane, 2-(4-sulfamoylphenylamino)quinazolin-8-yl trifluoromethanesulfonate (45 mg, 100 umole), $Pd(dppf)Cl_2$ (9 mg, 11 umole) and 2M Na_2CO_3 (300 ul, 600 umole) were added. The reaction mixture was stirred at 92°c for 5hr. The reaction mixture was poured into 30 ml of saturated

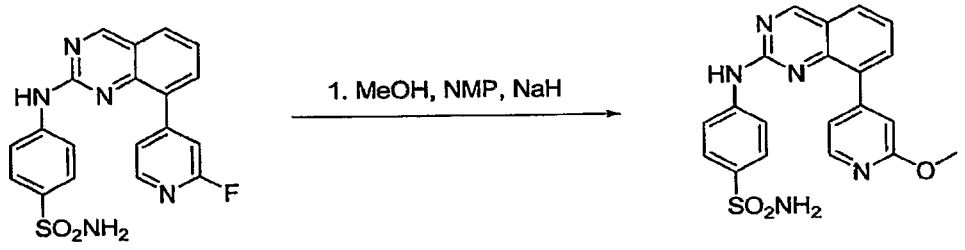
PP028218.0002

$NaHCO_3$ and extracted with ethyl acetate (2x50 ml). The combined organic layers were washed with water (2x20 ml) and brine (30 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown solid (150 mg) that then purified on prep HPLC to give 4-(8-(6-(2-(pyrrolidin-1-yl)ethylamino)-5-(trifluoromethyl)pyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide. as powder (2.7 mg). ES/MS *m/z* 558 (MH^+).

Example 56

Preparation of 4-(8-(2-methoxypyridin-4-yl)quinazoline-2-ylamino)benzenesulfonamide (Compound 418)

The subject compound was prepared according to the general Scheme below:



To a solution of 4-(8-(2-fluoroypyridin-4-yl)quinazoline-2-ylamino)benzenesulfonamide (9 mg, 0.0227 mMol) in NMP (0.4 ml) and MeOH (0.4mL) under argon was added (10eq.) NaH 60 % in oil. The reaction was sealed and heated at 65 °C for 5.5 hrs. The crude reaction mixture was concentrated under reduced pressure, purified on prep HPLC and lyophilized to give the desired product (1.2 mg) as TFA salt. ES/MS *m/z* 408 (MH^+).

Example 57

Synthesis of 4-(8-(6-fluoropyridin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide (Compound 413)

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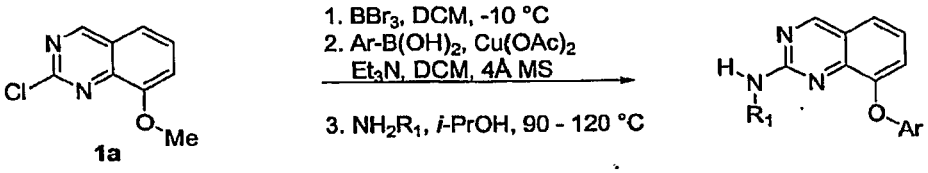

Step 1. To a 0.13 M solution of **1a** in DCM was added boron tribromide (2.0 eq. of a 1.0 M solution in DCM) dropwise at –10 °C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature (dark orange color) and stirred for 22 hours. The reaction was then cooled to 0 °C (red solution and precipitate formed) and the precipitate was collected by vacuum filtration and rinsed with cold DCM. The solid was stirred in ice water for one hour then filtered off, washed with water, cold 2-propanol and hexanes. The light tan solid was dried under vacuum to give the desired product in 82 % yield as a mixture of the 2-chloro and 2-bromoquinazolin-8-ol. ES/MS *m/z* 181.1 and 225.0/227.0 (MH^+).

Step 2. To a 0.1 M solution of the 2-chloro and 2-bromoquinazolin-8-ol in DCM was added 4Å MS followed by $Cu(OAc)_2 \cdot H_2O$ (1.0 eq.). The solution was stirred at room temperature for 5 min. (brown color), then 2-fluorpyridine5-boronic acid was added (2.0 eq.), followed by Et_3N (5 eq.). The solution turned dark green and it was allowed to stir for 24 hr. The reaction was then filtered, the filtrate was evaporated and passed through a plug of silica gel eluting with EtOAc. Upon concentration of the fractions, the desired product was obtained in 33% yield. ES/MS *m/z* 276.0 and 321.9/320.0 (MH^+).

Step 3. To a 0.13 M solution of the 2-chloro-8-(6-fluoropyridin-3-yloxy)quinazoline and 2-bromo-8-(6-fluoropyridin-3-yloxy)quinazoline mixture in *i*-PrOH was added sulfanilamide (1.0 eq.) and the solution was heated to refluxed for 12 hr. Cooled to room temperature and the precipitate was filtered off and washed with *i*-PrOH to give the desired product in 61% yield. The solid was 96% pure by HPLC. ES/MS *m/z* 412.0 (MH^+) for 595644 - 4-(8-(6-fluoropyridin-3-yloxy)quinazolin-2-ylamino)benzenesulfonamide.

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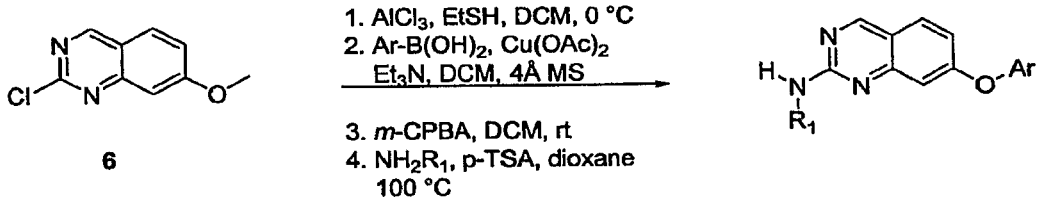
Example 58

Synthesis of 4-(7-(2-fluoropyridin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide (Compound 416)



6

Step 1. To a solution of DCM/ethanethiol (0.3 M, 1:1) was added $AlCl_3$ (6 eq.) and the reaction was cooled to 0 °C under a nitrogen atmosphere. Compound **6** was dissolved in DCM and added dropwise to the above solution dropwise. The reaction was allowed to warm to room temperature and stirred for 36 hr. The solvent was removed under vacuum and the crude was dissolved in EtOAc. Saturated $NaHCO_3$ was added slowly dropwise and the layers were separated. The organic layer was dried with brine and Na_2SO_4 and concentrated. The crude was triturated in DCM and the precipitate was filtered off to give the desired product as an off-white solid in 83% yield. ES/MS *m/z* 207.0 (MH^+).

Step 2. To a 0.1 M solution of the 2-(ethylthio)quinazolin-7-ol in DCM was added 4Å MS followed by $Cu(OAc)_2 \cdot H_2O$ (1.0 eq.). The solution was stirred at room temperature for 5 min. (brown color), then 2-fluoropyridine-5-boronic acid was added (2.0 eq.), followed by Et_3N (5 eq.). The solution turned dark green and it was allowed to stir for 24 hrs. The reaction was then filtered, the filtrate was evaporated and passed through a plug of silica gel eluting with EtOAc. Upon concentration of the fractions, the desired product was obtained in 41% yield. ES/MS *m/z* 302.0 (MH^+).

Step 3. To a 0.2 M solution of the 2-(ethylthio)-7-(2-fluoropyidin-4-yloxy)quinazoline in DCM was added *m*-CPBA (3 eq.) and the solution was stirred for 30 min at room temperature. Quenched the reaction with 1N $NaHCO_3$ and extracted with DCM. The organic layer was dried

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with Na_2SO_4 and concentrated. Purification via SiO_2 column chromatography eluting with EtOAc and Hexanes (50%) afforded the desired product in 53% yield. ES/MS *m/z* 334.0 (MH^+).

Step 4. To a 0.06 M solution of the 2-(ethylsulfonyl)-7-(2-fluoropyridin-4-yloxy)quinazoline in dioxane was added sulfanilamide (2.0 eq.) and *p*-TSA·H_2O (0.8 eq.) and the reaction was heated to 100 °C for 15 hr. The solvent was removed under vacuum and the crude was purified via automated reverse phase HPLC. The pure fractions were lyophilized over 2 days to afford the desired product 4-(7-(2-fluoropyridin-4-yloxy)quinazolin-2-ylamino)benzenesulfonamide in 31% yield as the TFA salt. ES/MS *m/z* 412.1 (MH^+).

BIOLOGICAL METHODS

I. PDK1 Kinase Alpha Screen Assay

Reagents/Concentrations: The PDK1-4 peptide substrate, biotin-GGGGRTWTLCG-NH2, was purchased from the Tufts University Core Facility. The final concentration of PDK1-4 peptide substrate was 50 nM The ATP substrate (Adenosine-5'-triphosphate) was purchased from Roche Diagnostics. The final concentration of ATP substrate was 10uM. Phospho-(Ser/Thr) PKA substrate antibody was purchased from Cell Signaling Technology. The final concentration of antibody was 0.3 mg/ml. The Alpha Screen Protein A detection kit containing donor and acceptor beads was purchased from PerkinElmer Life Sciences. The final concentration of both donor and acceptor beads was 25 μg/ml. Alpha Screen was used for detection. The biotinylated-PDK1-4 peptide was phosphorylated by PDK1 kinase using the ATP substrate. The biotinylated-PDK1-4 peptide substrate was bound to the streptavidin coated donor bead. The antibody was bound to the protein A coated acceptor bead. The antibody bound to the phosphorylated form of the biotinylated PDK-1 peptide substrate, bringing the donor and acceptor beads into close proximity. Laser irradiation of the donor bead at 680nm generated a flow of short-lived singlet oxygen molecules. When the donor and acceptor beads were in close proximity, the reactive oxygen generated by the irradiation of the donor beads initiated a luminescence/fluorescence cascade in the acceptor beads. This process led to a highly amplified signal with output in the 530-620 nm range. Assays were carried out in 50 mM Tris, pH=7.5, 10 mM $MgCl_2$, 0.1% Bovine Serum Albumin, 0.01% Tween-20, 2 mM Dithiolthreitol,

2.5% Dimethyl Sulfoxide. Reactions were stopped by adding 50 mM Tris, pH=7.5, 90 mM EDTA, 0.1% Bovine Serum Albumin, 0.01% Tween-20.

Procedure: To 10 µl of PDK1-4 peptide, 0.5 µl of test compound in dimethyl sulfoxide is added. PDK1 kinase and ATP are mixed. 10 µl of the PDK1 kinase/ATP mix is added to start the reaction. The reaction is allowed to proceed for 3-18 hours. The reactions are stopped by adding 10 µl of the EDTA-containing stop buffer. Beads are mixed with antibody. 25 µl of the bead/antibody mix is added to the stopped reactions. Plates are incubated at room temperature overnight to allow for detection development before being read. The assay is run is a 384-well format.

Results: Each of the compounds listed in Tables 1-5 was screened according the method above, and exhibited an IC_{50} value of less than or equal to 25 µM, with respect to inhibition of PDK1. Additionally, many of the compounds exhibited an IC_{50} of less than 10 µM, or less than 1 µM, or less than 0.1 µM, or less than 0.01 µM. Accordingly, each of the compounds is preferred individually, and/or as a member of a group that includes the compounds of Formula I, or Formula II or Formula III.

II. CDK1 (CDC2) Kinase Inhibition In Vitro Screen Assay

Reagents/Concentrations: Human full length Cdk1 is purchased from Upstate (# 14-450) as a co-purification with Cyclin B. The final enzyme concentration in the assay is 0.8 nM. Histone H1 peptide substrate is purchased from Research Genetics. The peptide, with the sequence lcBiotin-GGCGPKTPKKAKKL[CONH2], is used in the assay at a final concentration 0.5 µM. The ATP substrate (Adenosine-5'-triphosphate) was purchased from Roche Diagnostics. The final concentration of ATP substrate is 1 µM. P^{33} γ-ATP is purchased from NEN. The biotinylated peptide substrate is phosphorylated by Cdk1/Cyclin B enzyme, in the presence of varying concentrations of compounds, using the ATP substrate. A fraction of ATP in the reaction is radiolabeled to provide a detectable phosphorylation signal. The phosphoryaltion reaction is stopped with the addition of 25 mM EDTA. The solutions are then transferred to White BioBind Streptavidin Coated Assay plates, purchased from Thermo Electron Corporation. After washing, Microscint 20 scintillation fluid, purchased from Perkin Elmer, is added to each well and counts per minute (cpm) is measured using a Packard TopCount

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Microscintillation Counter. The highest cpms measured indicates the maximum phosphorylation of the substrate possible under the assay conditions. Reactions run without enzyme present give cpms indicative of complete inhibition of the enzyme. Each concentration of compound produces a measurable percent inhibition from the maximum signal based on these values. Assays were carried out in 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 1 mM DTT, 1 mM EGTA, 25 mM β-glycerol phosphate, 1 mM NaF, 0.01% BSA/PBS, 0.5 uM peptide substrate, and 0.8 nM Cdk1.

Procedure: Distribute 100 uL of Reaction Buffer containing 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 0.01% BSA/PBS, 1.5 mM DTT, 1.5 mM EGTA, 37.5 mM β-glycerol phosphate, 1.5 mM NaF, 0.75 uM peptide substrate, and 1.2 nM Cdk1 to each well. 100% inhibition control wells contain no Cdk1. Add compounds to wells in desired 10X concentrations with 10% DMSO, 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, and 0.01% BSA/PBS. Start reactions by adding 15 uL of ATP concentrated at 10 uM, with P^{33} γ-ATP at < 10 nM as label. Run reactions for four hours at room temperature with shaking. Streptavidin coated plates are blocked for one hour with 1% BSA in PBS. 100 uL 50 mM EDTA is added to each streptavidin well. 100 uL of each assay solution are transferred to corresponding streptavidin wells containing EDTA. Capture of radiolabeled substrate then takes place by shaking at room temperature for one hour. After binding the wells are washed 4 times with PBS, 200 uL Microscint 20 is added to each well, and cpms are measured. The assay is run in a 96-well format.

Results: Many of the compounds listed in Tables 1-5 were screened according to the method above, and exhibited an IC_{50} value of less than or equal to 25 μM, with respect to inhibition of Cdk1. Additionally, many of the compounds exhibited an IC_{50} of less than 10 μM, or less than 1 μM, or less than 0.1 μM. Accordingly, each of the compounds is preferred individually, and/or as a member of a group that includes the compounds of Formula I, or Formula II or Formula III.

III. CDK2 Kinase Inhibition In Vitro Screen Assay

Reagents/Concentrations: Human full length Cdk2 is purchased from Upstate (# 14-407) as a co-purification with Cyclin A. The final enzyme concentration in the assay is 5 nM.

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Histone H1 peptide substrate is purchased from Research Genetics. The peptide, with the sequence lcBiotin-GGCGPKTPKKAKKL[CONH2], is used in the assay at a final concentration 0.5 μM. The ATP substrate (Adenosine-5'-triphosphate) was purchased from Roche Diagnostics. The final concentration of ATP substrate is 1 μM. P^{33} γ-ATP is purchased from NEN. The biotinylated peptide substrate is phosphorylated by Cdk2/Cyclin A enzyme, in the presence of varying concentrations of compounds, using the ATP substrate. A fraction of ATP in the reaction is radiolabeled to provide a detectable phosphorylation signal. The phosphoryaltion reaction is stopped with the addition of 25 mM EDTA. The solutions are then transferred to White BioBind Streptavidin Coated Assay plates, purchased from Thermo Electron Corporation. After washing, Microscint 20 scintillation fluid, purchased from Perkin Elmer, is added to each well and counts per minute (cpm) is measured using a Packard TopCount Microscintillation Counter. The highest cpms measured indicates the maximum phosphorylation of the substrate possible under the assay conditions. Reactions run without enzyme present give cpms indicative of complete inhibition of the enzyme. Each concentration of compound produces a measurable percent inhibition from the maximum signal based on these values. Assays were carried out in 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 1 mM DTT, 1 mM EGTA, 25 mM β-glycerol phosphate, 1 mM NaF, 0.01% BSA/PBS, 0.5 uM peptide substrate, and 5 nM Cdk1.

Procedure: Distribute 100 uL of Reaction Buffer containing 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 0.01% BSA/PBS, 1.5 mM DTT, 1.5 mM EGTA, 37.5 mM β-glycerol phosphate, 1.5 mM NaF, 0.75 uM peptide substrate, and 7.5 nM Cdk2 to each well. 100% inhibition control wells contain no Cdk2. Add compounds to wells in desired 10X concentrations with 10% DMSO, 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, and 0.01% BSA/PBS. Start reactions by adding 15 uL of ATP concentrated at 10 uM, with P^{33} γ-ATP at < 10 nM as label. Run reactions for four hours at room temperature with shaking. Streptavidin coated plates are blocked for one hour with 1% BSA in PBS. 100 uL 50 mM EDTA is added to each streptavidin well. 100 uL of each assay solution are transferred to corresponding streptavidin wells containing EDTA. Capture of radiolabeled substrate then takes place by shaking at room temperature for one hour. After binding the wells are washed 4 times with PBS, 200 uL Microscint 20 is added to each well, and cpms are measured. The assay is run in a 96-well format.

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Results: Many of the compounds listed in Tables 1-5 were screened according to the method above, and exhibited an IC_{50} value of less than or equal to 25 μM, with respect to inhibition of Cdk2. Additionally, many of the compounds exhibited an IC_{50} of less than 10 μM, or less than 1 μM, or less than 0.1 μM. Accordingly, each of the compounds is preferred individually, and/or as a member of a group that includes the compounds of Formula I, Formula II or Formula III.

IV. Cell Proliferation Assay Protocol:

A2780, PC-3, or PC3MM cells were seeded at 1000 cells/well in 100 μL/well (10.000 cells/mL) growth media in 96-well plates. Cells were allowed to adhere to the bottom of plates for 3-5 hours in a 37 °C 5% CO_2 incubator. Compounds were dissolved in DMSO and then transferred to the cell plates. The cells were incubated with the compounds for 3 days in a 37 °C 5% CO_2 incubator. The growth medium containing the compounds was then removed from the cells and fresh medium was added, followed by 100 μL of Cell Titer Glo assay reagent (Promega). This mixture was shaken for 1 minute and then incubated without shaking for 10 minutes. Activity determinations for the compounds were made by detection on a Trilux Instrument.

Results: Many of the compounds listed in Tables 1-5 were screened according to the method above, and exhibited an EC_{50} value of less than or equal to 10 μM, with respect to inhibition of cell proliferation. Additionally, many of the compounds exhibited an IC_{50} of less than 5 μM, or less than 1 μM, or less than 0.1 μM.

V. Cell Proliferation Assay Protocol: PC-3 Cell Line

PC-3 cells were seeded at 1000 cells/well in 100 μL/well (10.000 cells/mL) along with growth media into black-walled, clear bottom 96-well plates. The cells were allowed to adhere to the bottom of the plate for 3-5 hours in a 37 °C 5% CO_2 incubator.

Test compounds were diluted to 500x in DMSO. The DMSO solutions of six of the compounds were transferred to the cells in the 96 well round bottom plate, column 2, row B-F. A 1:3 serial dilution of each compound was carried out. The serial dilution comprised adding 20 μL of DMSO to the wells containing the compounds and doing a 1:3 dilution across the plate

from columns 2-10. Column 11 contained only DMSO. The serial dilution was carried out using a BioMek 2000 protocol "CP Serial Dilution using 250 μL tips" or "Proliferation Compound" (if using 20 μL tips).

To a 96 deep well block, columns 2-11 rows B-F, was transferred 500 μL of growth medium. Using the FX protocol "HH_CellAssay_2μL to 500 μL", 2 μL of compound from each cell of the compound plate was transferred to the corresponding cell in the 96 deep well block containing 500 μL of growth medium. The instrument was programmed to dilute the compound in growth medium and then transfer 100 μL of that mixture to cell plates containing cells. The cell plates, to which test compounds had been added, were incubated for 3 days at 37 °C. Following the incubation, the medium was removed and replaced with fresh medium. Cell Titer Glo (100 μL) was added to each well and the plate was shaken for 1 minute and then incubated without shaking for 10 minutes. The plates were then read using a Trilux instrument.

VI. The $pAkt^{T308}$ ECL Assay Protocol

On Day 1, PC-3 cells were seeded at 15,000 cells/well in 100 μL/well (10.000 cells/mL) growth media into black-walled, clear bottom, poly-L-lysine coated plates. The cells were incubated overnight in a 37 °C, 5% CO_2 incubator.

On Day 2, a MSD ECL plate was blocked for two hours with 150 μL per well of 3% MSD blocker A.

Test compounds were diluted to 500x in DMSO and then were subjected to further serial dilution using a BioMek 2000 instrument. DMSO diluted compounds were then diluted into growth media and then added to the cell plates.

The cell plates incubated with compounds for six hours in a 37 °C, 5% CO_2 incubator after which the growth medium was removed and 55 μl of MSD lysis buffer was added to cell plates on ice. The plates were lysed on ice for five minutes followed by 15 minutes of vigorous shaking on a plate shaker at 4 °C. The blocked MSD assay plates were washed twice with 1x MSD wash buffer followed by the addition of cell lysate as follows: 30 μl of cell lysate was added to the pAkt308 plates and 13 μl of lysate + 12 μl lysis buffer was added to the tAkt plates. The plates were then sealed and shaken at 4 °C overnight.

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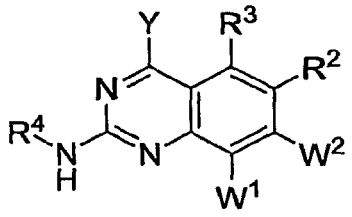
On Day 3, the MSD plates were washed four times with 1x MSD wash buffer then, 25 µl/well of MSD SULFO-TAG antibodies diluted to 10nM final concentration in 1% blocker. A buffer was added to the antibody diluent which was added to assay plates. The plates were then sealed and incubated at RT for 1.5 hour. The plates were then washed twice with 1x MSD wash buffer followed by the addition of 150µl/well of 1.5x MSD read buffer. The plates were read immediately after the addition of read buffer using a Trilux instrument.

Many of tested compounds demonstrated IC_{50} values of less than 5 µM, as shown in Table 1. Some of them even had IC_{50} values as low as less than 5 µM.

The contents of each of the patents, patent applications and journal articles cited above are hereby incorporated by reference herein and for all purposes as if fully set forth in their entireties.

What is claimed is:

1. A compound of Formula I:



I

wherein:

one of W^1 or W^2 is R^1 and the other is $-L-A^1$;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl;

A^1 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, or substituted heterocyclyl;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl,

substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl,

provided when R^4 is heteroaryl or substituted heteroaryl, W^2 is not aryl or heteroaryl; or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

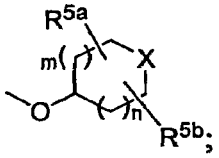
2. A compound of claim 1, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is substituted phenyl.

3. A compound of claim 1, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with a group of formula $-X^1-N(R_{501})(R_{502})$; wherein X^1 is a covalent bond, SO_2, or C(=O); and R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl;

or R_{501} and R_{502}, taken together with the nitrogen atom to which they are attached, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

4. A compound of claim 3, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein $-N(R_{501})(R_{502})$ forms $-NH_2$, $-NH-CH(CH_3)_2$, $-NH-(CH_2)_2-O-CH_3$, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or $-NH-(CH_2)_2$-pyrrolidin-1-yl.

5. A compound of claim 1, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein $-L-A^1$ is a heterocyclyloxy group having the structure:



wherein,

X is O or NR^6;

R^{5a} and R^{5b} are each independently H, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, or substituted amino;

R^6 is H, acyl, substituted carbonyl, sulfonyl, alkyl, or substituted alkyl;

or R^{5a} and R^6 are taken together to form a bridging alkylene moiety;

or R^{5a} and R^{5b} are taken together to form a bridging alkylene moiety;

m and n are independently 0, 1 or 2.

6. A compound of claim 5, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein W^1 is R^1 and W^2 is $-L-A^1$.

7. A compound of claim 6, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with a group of formula $-X^1-N(R_{501})(R_{502})$; wherein X^1 is a covalent bond, SO_2, or C(=O); and R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl;

or R_{501} and R_{502}, taken together with the nitrogen atom to which they are attached, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

8. A compound of claim 7, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein $-N(R_{501})(R_{502})$ forms $-NH_2$, $-NH-CH(CH_3)_2$, $-NH-(CH_2)_2-O-CH_3$, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or $-NH-(CH_2)_2$-pyrrolidin-1-yl.

9. A compound of claim 8, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^2 is heteroaryl or substituted heteroaryl.

10. A compound of claim 5, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein W^1 is $-L-A^1$ and W^2 is R^1.

11. A compound of claim 10, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with a group of formula $-X^1-N(R_{501})(R_{502})$; wherein X^1 is a covalent bond, SO_2, or C(=O); and R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl;

or R_{501} and R_{502}, taken together with the nitrogen atom to which they are attached, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

12. A compound of claim 11, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein $-N(R_{501})(R_{502})$ forms $-NH_2$, $-NH-CH(CH_3)_2$, $-NH-(CH_2)_2-O-CH_3$, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or $-NH-(CH_2)_2$-pyrrolidin-1-yl.

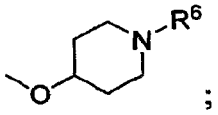
13. A compound of claim 12, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^2 is heteroaryl or substituted heteroaryl.

14. A compound of claim 5, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1 is H, halogen, cyano; or

phenyl optionally substituted with $-C(=O)-N(R^{501})(R^{502})$; or

a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms independently selected from O, S and N, that is optionally substituted with up to three substituents selected from alkyl, alkoxy and $-N(R^{501})(R^{502})$; or

a group of formula:



;

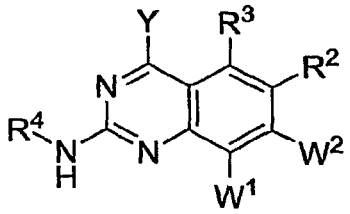
wherein each R_{501} and each R_{502} is independently selected from H, alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl.

15. A compound of claim 1, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein W^1 is heteroaryl or substituted heteroaryl.

16. A compound of claim 1, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein W^2 is heteroaryl or substituted heteroaryl.

17. A compound of claim 1, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^2 is heteroaryl or substituted heteroaryl.

18. A compound of Formula I:



I

wherein:

one of W^1 or W^2 is R^1 and the other is $-L-A^1$;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl;

A^1 is hydroxyl, amino, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cyclyl, or substituted cyclyl, heterocyclyl, or substituted heterocyclyl, provided whenW^2 is hydroxyl or methoxy, A^1 is not isopropyl or cyclopentyl;

Y is H, C_{1-3} alkyl, halo, cyano, nitro, or amino;

R^1 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclyloxy, and substituted heterocyclyloxy;

R^2 and R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; and

R^4 is aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

19. A compound of claim 18, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein A^1 is alkyl or substituted alkyl.

20. A compound of claim 18, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein A^1 is hydroxyl or amino.

21. A compound of claim 18, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is phenyl or substituted phenyl.

22. A compound of claim 21, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with a group of formula $-X^1$-$N(R_{501})(R_{502})$; wherein X^1 is a covalent bond, SO_2, or C(=O); and R_{501} and R_{502} are independently selected from H, alkyl, substituted alkyl, alkoxyalkyl, cycloalkyl and heterocyclylalkyl;

or R_{501} and R_{502}, taken together with the nitrogen atom to which they are attached, form a heterocyclyl group that is optionally substituted with up to three groups independently selected from C_{1-3} alkyl, hydroxyl, halo, alkoxy, amino, and substituted amino.

23. A compound of claim 22, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein $-N(R_{501})(R_{502})$ forms $-NH_2$, $-NH-CH(CH_3)_2$, $-NH-(CH_2)_2-O-CH_3$, -NH-cyclopropyl, morpholin-4-yl, 4-methyl-piperizine-1-yl, or $-NH-(CH_2)_2$-pyrrolidin-1-yl.

24. A compound of claim 21, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein A^1 is alkyl or substituted alkyl.

25. A compound of claim 21, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein A^1 is hydroxyl or amino.

26. A compound of claim 18, a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is heteroaryl or substituted heteroaryl.

27. A method of inhibiting PDK1 comprising administering to a human or animal subject, a compound of any one of the previous claims.